STN SEARCH TRANSCRIPT 10/828,354

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 NEWS  1          Web Page URLs for STN Seminar Schedule - N. America
 NEWS  2          "Ask CAS" for self-help around the clock
 NEWS  3  AUG 09  INSPEC enhanced with 1898-1968 archive
 NEWS  4  AUG 28  ADISCTI Reloaded and Enhanced
 NEWS  5  AUG 30  CA(SM)/CAplus(SM) Austrian patent law changes
 NEWS  6  SEP 11  CA/CAplus enhanced with more pre-1907 records
 NEWS  7  SEP 21  CA/CAplus fields enhanced with simultaneous left and right
                  truncation
 NEWS  8  SEP 25  CA(SM)/CAplus(SM) display of CA Lexicon enhanced
 NEWS  9  SEP 25  CAS REGISTRY(SM) no longer includes Concord 3D coordinates
 NEWS 10  SEP 25  CAS REGISTRY(SM) updated with amino acid codes for pyrrolysine
 NEWS 11  SEP 28  CEABA-VTB classification code fields reloaded with new
                  classification scheme
 NEWS 12  OCT 18  The Derwent World Patents Index suite of databases on STN will
                  be enhanced and reloaded on October 22, 2006

 NEWS EXPRESS  JUNE 30 CURRENT WINDOWS VERSION IS V8.01b, CURRENT
               MACINTOSH VERSION IS V6.0c(ENG) AND V6.0Jc(JP),
               AND CURRENT DISCOVER FILE IS DATED 26 JUNE 2006.

 NEWS HOURS    STN Operating Hours Plus Help Desk Availability
 NEWS LOGIN    Welcome Banner and News Items
 NEWS IPC8     For general information regarding STN implementation of IPC 8
 NEWS X25      X.25 communication option no longer available

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FILE 'HOME' ENTERED AT 06:22:43 ON 19 OCT 2006

=> file reg
COST IN U.S. DOLLARS                                SINCE FILE      TOTAL
                                                       ENTRY     SESSION
FULL ESTIMATED COST                                     1.05        1.05

FILE 'REGISTRY' ENTERED AT 06:25:50 ON 19 OCT 2006
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STRUCTURE FILE UPDATES:   18 OCT 2006  HIGHEST RN 910777-14-9
DICTIONARY FILE UPDATES:  18 OCT 2006  HIGHEST RN 910777-14-9

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http://www.cas.org/ONLINE/UG/regprops.html

=>
Uploading C:\Program Files\Stnexp\Queries\SODIUM CHANNEL PYRAZINE DIV.str
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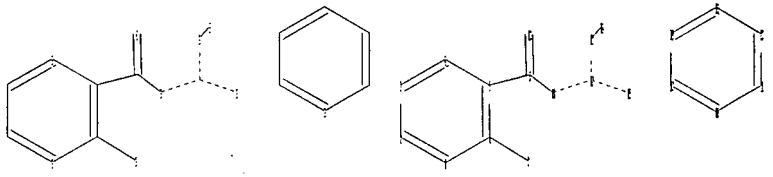

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chain nodes :
7  9  10  11  12  13  14  15
ring nodes :
1  2  3  4  5  6  16  17  18  19  20  21
chain bonds :
5-9  6-7  9-10  9-11  11-12  12-13  12-15  13-14
ring bonds :
1-2  1-6  2-3  3-4  4-5  5-6  16-17  16-21  17-18  18-19  19-20  20-21
exact/norm bonds :
6-7  9-10  9-11  11-12  12-13  12-15
exact bonds :
5-9  13-14
normalized bonds :
1-2  1-6  2-3  3-4  4-5  5-6  16-17  16-21  17-18  18-19  19-20  20-21
isolated ring systems :
containing 1 : 16 :


Match level :
1:Atom  2:Atom  3:Atom  4:Atom  5:Atom  6:Atom  7:CLASS  9:CLASS  10:CLASS
11:CLASS  12:CLASS  13:CLASS  14:CLASS  15:CLASS  16:Atom  17:Atom  18:Atom
19:Atom  20:Atom  21:Atom



L1      STRUCTURE UPLOADED

=> D L1
L1 HAS NO ANSWERS
L1              STR
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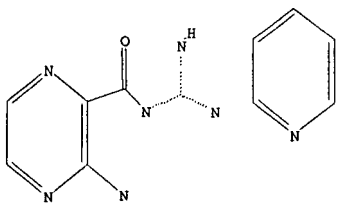

Structure attributes must be viewed using STN Express query preparation.

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SAMPLE SCREEN SEARCH COMPLETED -        3 TO ITERATE

100.0% PROCESSED         3 ITERATIONS                                0 ANSWERS
SEARCH TIME: 00.00.01

FULL FILE PROJECTIONS:   ONLINE  **COMPLETE**
                         BATCH   **COMPLETE**
PROJECTED ITERATIONS:             3 TO      163
PROJECTED ANSWERS:                0 TO        0

L2             0 SEA SSS SAM L1

=> S L1 SSS FULL
FULL SEARCH INITIATED 06:26:22 FILE 'REGISTRY'
FULL SCREEN SEARCH COMPLETED -       71 TO ITERATE

100.0% PROCESSED        71 ITERATIONS                               15 ANSWERS
SEARCH TIME: 00.00.05

L3            15 SEA SSS FUL L1

=> FILE CAPLUS
COST IN U.S. DOLLARS                          SINCE FILE      TOTAL
                                                 ENTRY    SESSION
FULL ESTIMATED COST                            166.94     167.99

FILE 'CAPLUS' ENTERED AT 06:26:31 ON 19 OCT 2006
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FILE COVERS 1907 - 19 Oct 2006  VOL 145 ISS 17
FILE LAST UPDATED: 17 Oct 2006  (20061017/ED)

Effective October 17, 2005, revised CAS Information Use Policies apply.
They are available for your review at:

http://www.cas.org/infopolicy.html

=> S L3
L4          20 L3

=> D 1-20 IBIB ABS HITSTR

L4   ANSWER 1 OF 20  CAPLUS  COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER:         2006:886342  CAPLUS
DOCUMENT NUMBER:          145:293103
TITLE:                    Preparation of herteroaryl substituted
                          pyrazinyl-piperazine-piperidines with CXCR3 antagonist
                          activity
INVENTOR(S):              Zeng, Qingbei; Yang, De-Yi; Rosenblum, Stuart B.;
                          Wong, Michael K. C.; Anilkumar, Gopinadhan N.; Kim,
                          Seong Heon; Yu, Wensheng; Kozlowski, Joseph A.; Shih,
                          Neng-Yang; Mcguinness, Brian F.; Zawacki, Lisa Guise;
                          Hobbs, Douglas W.
PATENT ASSIGNEE(S):       Schering Corporation, USA; Pharmacopeia Drug
                          Discovery, Inc.
SOURCE:                   PCT Int. Appl., 187pp.
                          CODEN: PIXXD2
DOCUMENT TYPE:            Patent
LANGUAGE:                 English
FAMILY ACC. NUM. COUNT:   1
PATENT INFORMATION:

     PATENT NO.          KIND   DATE        APPLICATION NO.         DATE
     ----------          ----   --------    -------------------     --------
     WO 2006091428        A2    20060831    WO 2006-US5122          20060214
         W:  AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH,
             CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD,
             GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR,
             KZ, LC, LK, LR, LS, LT, LU, LV, LY, MA, MD, MG, MK, MN, MW, MX,
             MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE,
             SG, SK, SL, SM, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC,
             VN, YU, ZA, ZM, ZW
         RW: AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE,
             IS, IT, LT, LU, LV, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ,
             CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG, BW, GH,
             GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY,
             KG, KZ, MD, RU, TJ, TM
PRIORITY APPLN. INFO.:                        US 2005-653477P     P  20050216
GI

* STRUCTURE DIAGRAM TOO LARGE FOR DISPLAY -  AVAILABLE VIA OFFLINE PRINT *

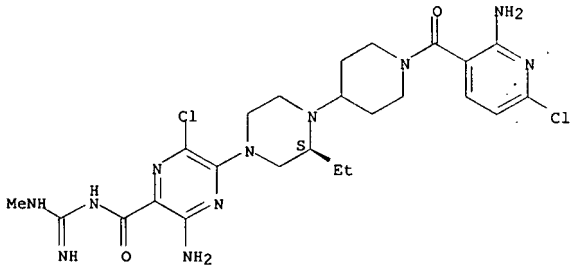
AB   Title compds. I [X = N, O, alkyl, etc.; D = (un)substituted cycloalkyl,
     cycloalkenyl, aryl (excluding phenyl), etc.; Y = CO, CH-heteroaryl,
     (un)substituted imine, etc.; R1 and R2 independently = H, alkyl,
     hydroxyalkyl, etc.; R3 and R6 = H, alkyl, CN, haloalkyl, etc.; R7 and R8
     independently = H, OH, CN, alkoxy, etc.; R10 independently at each
     occurrence = H, aryl, heteroaryl, etc.; R11 = H, CO2H, halo, etc.; R12 =
     H, CN , hydroxyalkyl, etc.; m = 0-4; n = 0-4], and their pharmaceutically
     acceptable salts, are prepared and disclosed as CXCR3 antagonists.  Thus,
     e.g., II was prepared N-acylation of piperidine III (preparation given) with
     lithium 2-amino-5-chloronicotinate (preparation given).  In assays for CXCR3
     antagonist activity, selected compds. were found to demonstrate Ki values
     from 1-4 nM.  Also disclosed is a method of treating chemokine mediated
```

diseases, such as, palliative therapy, curative therapy, prophylactic therapy of certain diseases and conditions such as inflammatory diseases (non limiting example(s) include, psoriasis), autoimmune diseases (non limiting example(s) include, rheumatoid arthritis, multiple sclerosis), graft rejection (non limiting example(s) include, allograft rejection, xenograft rejection), infectious diseases (e.g , tuberculoid leprosy), fixed drug eruptions, cutaneous delayed type hypersensitivity responses, ophthalmic inflammation, type I diabetes, viral meningitis and tumors using I.

IT *908344-68-3P 908344-70-7P 908344-72-9P*
908344-81-0P 908345-56-2P
RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(preparation of herteroaryl substituted pyrazinyl-piperazine-piperidines with CXCR3 antagonist activity)

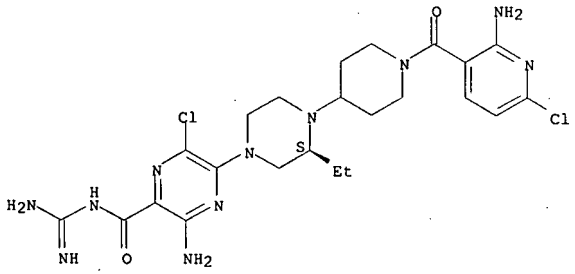
RN 908344-68-3 CAPLUS
CN INDEX NAME NOT YET ASSIGNED

Absolute stereochemistry.



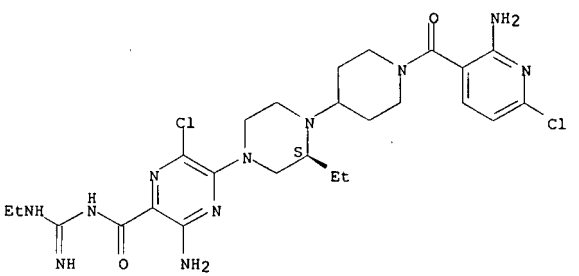
RN 908344-70-7 CAPLUS
CN INDEX NAME NOT YET ASSIGNED

Absolute stereochemistry.



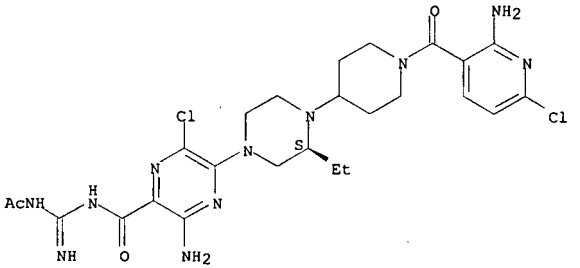
RN 908344-72-9 CAPLUS
CN INDEX NAME NOT YET ASSIGNED

Absolute stereochemistry.



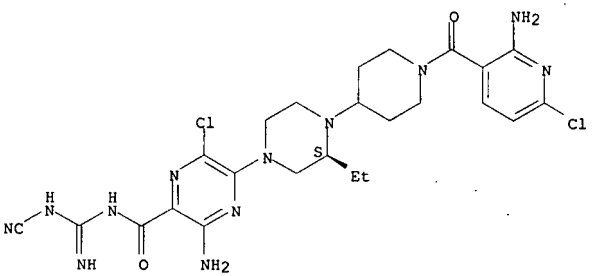
RN 908344-81-0 CAPLUS
CN INDEX NAME NOT YET ASSIGNED

Absolute stereochemistry.



RN 908345-56-2 CAPLUS
CN INDEX NAME NOT YET ASSIGNED

Absolute stereochemistry.



L4 ANSWER 2 OF 20 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2005:325702 CAPLUS
DOCUMENT NUMBER: 142:367646

TITLE: Methods using sodium channel blockers for reducing risk of infection from pathogens
INVENTOR(S): Johnson, Michael R.; Hopkins, Samuel E.
PATENT ASSIGNEE(S): USA
SOURCE: U.S. Pat. Appl. Publ., 52 pp.
CODEN: USXXCO
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 2005080093	A1	20050414	US 2004-920484	20040818
AU 2004287352	A1	20050519	AU 2004-287352	20040819
CA 2534069	AA	20050519	CA 2004-2534069	20040819
WO 2005044180	A2	20050519	WO 2004-US26778	20040819
WO 2005044180	A3	20051006		
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW				
RW: BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
EP 1656022	A2	20060517	EP 2004-816810	20040819
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, HU, PL, SK, HR				

PRIORITY APPLN. INFO.:

US 2003-496482P	P	20030820
US 2004-920484	A	20040818
WO 2004-US26778	W	20040819

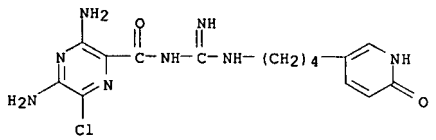
OTHER SOURCE(S): MARPAT 142:367646

AB Prophylactic treatment methods are provided for protection of individuals and/or populations against infection from airborne pathogens. In particular, prophylactic treatment methods are provided comprising administering a sodium channel blocker or pharmaceutically acceptable salt thereof to one or more members of a population at risk of exposure to or already exposed to one or more airborne pathogens, either from natural sources or from intentional release of pathogens into the environment.

IT *583825-20-1*
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(sodium channel blockers for reducing risk of infection from pathogens)

RN 583825-20-1 CAPLUS

CN Pyrazinecarboxamide, 3,5-diamino-6-chloro-N-[[[4-(1,6-dihydro-6-oxo-3-pyridinyl)butyl]amino]iminomethyl]- (9CI) (CA INDEX NAME)



L4 ANSWER 3 OF 20 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2003:678615 CAPLUS

DOCUMENT NUMBER: 139:191482
TITLE: Sodium channel blockers
INVENTOR(S): Johnson, Michael R.
PATENT ASSIGNEE(S): USA
SOURCE: PCT Int. Appl., 66 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

APPLICANT.

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2003070184	A2	20030828	WO 2003-US4823	20030219
WO 2003070184	A3	20040617		
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
US 2003195160	A1	20031016	US 2002-76551	20020219
US 6858614	B2	20050222		
CA 2476837	AA	20030828	CA 2003-2476837	20030219
AU 2003215286	A1	20030909	AU 2003-215286	20030219
EP 1485359	A2	20041215	EP 2003-711105	20030219
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, HU, SK				
JP 2005526726	T2	20050908	JP 2003-569144	20030219
US 2004198744	A1	20041007	US 2004-828278	20040421
US 2004198745	A1	20041007	US 2004-828329	20040421
US 2004198746	A1	20041007	~~US 2004-828353~~	20040421
US 2004198747	A1	20041007	US 2004-828354	20040421
US 2004204424	A1	20041014	~~US 2004-828235~~	20040421

PRIORITY APPLN. INFO.:

US 2002-76551	A	20020219
WO 2003-US4823	W	20030219

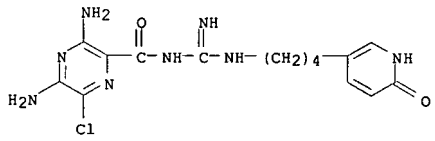
OTHER SOURCE(S): MARPAT 139:191482

AB The present invention relates to sodium channel blockers (Markush structures are included). The present invention also includes a variety of methods of treatment using these novel sodium channel blockers.

IT *583825-20-1P 583825-21-2P*
RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(sodium channel blockers for therapy of pulmonary and other diseases)

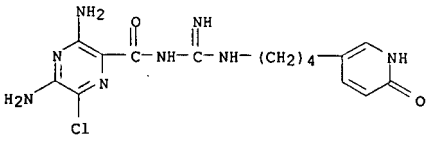
RN 583825-20-1 CAPLUS

CN Pyrazinecarboxamide, 3,5-diamino-6-chloro-N-[[[4-(1,6-dihydro-6-oxo-3-pyridinyl)butyl]amino]iminomethyl]- (9CI) (CA INDEX NAME)



RN 583825-21-2 CAPLUS

CN Pyrazinecarboxamide, 3,5-diamino-6-chloro-N-[[[4-(1,6-dihydro-6-oxo-3-pyridinyl)butyl]amino]iminomethyl]-, monohydrochloride (9CI) (CA INDEX NAME)



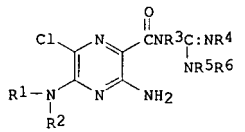
● HCl

L4 ANSWER 4 OF 20 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 1993:449413 CAPLUS
DOCUMENT NUMBER: 119:49413
TITLE: New pyrazine derivatives, their preparation and their use as ingredients in drugs
INVENTOR(S): Koeppe, Herbert; Speck, Georg; Stockhaus, Klaus
PATENT ASSIGNEE(S): Boehringer Ingelheim International G.m.b.H., Germany; Boehringer Ingelheim KG
SOURCE: PCT Int. Appl., 37 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: German
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9304048	A1	19930304	WO 1992-EP1738	19920731
W: AT, AU, BB, BG, BR, CA, CH, CS, DE, DK, ES, FI, GB, HU, JP, KP, KR, LK, LU, MG, MN, MW, NL, NO, PL, RO, RU, SD, SE, US				
RW: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LU, MC, NL, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, SN, TD, TG				
DE 4127026	A1	19930218	DE 1991-4127026	19910816
DE 4130461	A1	19930318	DE 1991-4130461	19910913
AU 9223870	A1	19930316	AU 1992-23870	19920731
AU 669122	B2	19960530		
EP 598770	A1	19940601	EP 1992-916697	19920731
EP 598770	B1	19971015		
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE				
JP 06509798	T2	19941102	JP 1992-504057	19920731
NO 9400523	A	19940215	NO 1994-523	19940215

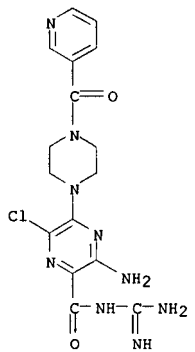
PRIORITY APPLN. INFO.: DE 1991-4127026 A 19910816
DE 1991-4130461 A 19910913
WO 1992-EP1738 A 19920731

OTHER SOURCE(S): CASREACT 119:49413; MARPAT 119:49413
GI



I

AB A process for the preparation of pyrazine derivative I where R1 = H or alkyl, R2 = functionalized alkyl moiety, R3, R5 = H and R4, R6 = H, Me, Et, Bu, benzyl was accomplished by conventional methods. E.g., reaction of 4.44 g of Me 3-amino-5,6-dichloropyrazine-2-carboxylate and 3.6 g of 2-amino-1-(2,6-dimethylphenoxy)propane with 2.2 g Et3N in 40 mL anhydrous DMF gave an intermediate pyrazinecarboxylic acid ester which underwent subsequent ammonolysis in 50 mL MeOH and 80mL of methanolic guanidine solution and eluted on silica gel by AcOH:i-PrOH:NH3 eluent to give N-amidino-3-amino-6-chloro-5-(2-[1-(2,6-dimethylphenoxy)]propylamino)pyrazine-2-carboxamide-hydrochloride. The products are suitable for use as active ingredients in drugs (no data).
IT *147932-18-1P*
RL: SPN (Synthetic preparation); PREP (Preparation)
(preparation of)
RN 147932-18-1 CAPLUS
CN Pyrazinecarboxamide, 3-amino-N-(aminoiminomethyl)-6-chloro-5-[4-(3-pyridinylcarbonyl)-1-piperazinyl]- (9CI) (CA INDEX NAME)

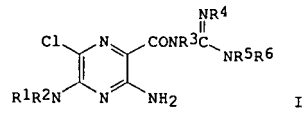


L4 ANSWER 5 OF 20 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 1993:408831 CAPLUS
DOCUMENT NUMBER: 119:8831
TITLE: Preparation of 2-guanidinocarbonyl-3,5-diamino-6-chloropyrazines as drugs
INVENTOR(S): Koeppe, Herbert; Speck, Georg; Stockhaus, Klaus
PATENT ASSIGNEE(S): Boehringer Ingelheim KG, Germany
SOURCE: Ger. Offen., 19 pp.
CODEN: GWXXBX
DOCUMENT TYPE: Patent
LANGUAGE: German

FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
DE 4127026	A1	19930218	DE 1991-4127026	19910816
WO 9304048	A1	19930304	WO 1992-EP1738	19920731
W: AT, AU, BB, BG, BR, CA, CH, CS, DE, DK, ES, FI, GB, HU, JP, KP, KR, LK, LU, MG, MN, MW, NL, NO, PL, RO, RU, SD, SE, US				
RW: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LU, MC, NL, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, SN, TD, TG				
AU 9223870	A1	19930316	AU 1992-23870	19920731
AU 669122	B2	19960530		
EP 598770	A1	19940601	EP 1992-916697	19920731
EP 598770	B1	19971015		
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE				
JP 06509798	T2	19941102	JP 1992-504057	19920731
HU 67661	A2	19950428	HU 1994-430	19920731
CZ 280760	B6	19960417	CZ 1994-337	19920731
AT 159250	E	19971115	AT 1992-916697	19920731
ES 2108129	T3	19971216	ES 1992-916697	19920731
RU 2124008	C1	19981227	RU 1994-15265	19920731
ZA 9206132	A	19930331	ZA 1992-6132	19920814
NO 9400523	A	19940215	NO 1994-523	19940215
PRIORITY APPLN. INFO.:			DE 1991-4127026 A	19910816
			DE 1991-4130461 A	19910913
			WO 1992-EP1738 A	19920731

OTHER SOURCE(S): MARPAT 119:8831
GI



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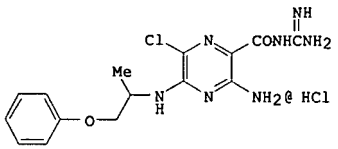
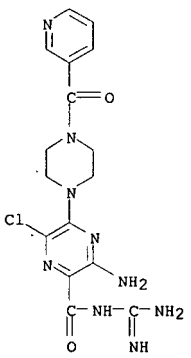


II

AB Title compds. [I; R1 = H, alkyl; R2 = morpholino, (substituted) alkyl, 4-piperidinyl, amidino; R1R2N = (substituted) piperidinyl, piperazinyl; R3-R6 = H, alkyl, PhCH2], effective inhibitors of Na+/H+ and Na+/Li+ exchange useful as antihypertensives, mucolytics, diuretics, neoplasm inhibitors, and platelet activating factor antagonists (no data), are prepared Thus, Me 3-amino-5,6-dichloropyrazine-2-carboxylate, 2-amino-1-(2,6-dimethylphenoxy)propane, and Et3N were heated in DMF at 95-100° for 1.5 h to give Me 3-amino-6-chloro-5-[2-[1-(2,6-dimethylphenoxy)]propylamino}pyrazine-2-carboxylate. This was heated with guanidine in MeOH to give title compound II.

IT *147932-18-1P*
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(preparation of, as drug)

RN 147932-18-1 CAPLUS
CN Pyrazinecarboxamide, 3-amino-N-(aminoiminomethyl)-6-chloro-5-[4-(3-pyridinylcarbonyl)-1-piperazinyl]- (9CI) (CA INDEX NAME)

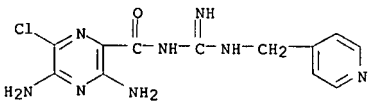


L4 ANSWER 6 OF 20 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 1988:583053 CAPLUS
DOCUMENT NUMBER: 109:183053
TITLE: Amiloride analogs cause endothelium-dependent relaxation in the canine coronary artery in vitro: possible role of sodium/calcium exchange
AUTHOR(S): Cocks, T. M.; Little, P. J.; Angus, J. A.; Cragoe, E. J., Jr.
CORPORATE SOURCE: Baker Med. Res. Inst., Prahran, 3181, Australia
SOURCE: British Journal of Pharmacology (1988), 95(1), 67-76
CODEN: BJPCBM; ISSN: 0007-1188
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The effect of amiloride analogs in endothelium-dependent relaxations were studied. The analogs used were those substituted on either the 5-amino group or the terminal guanidino nitrogen atom. The former block both Na+/Ca2+ and Na+/H+ exchange, while the latter block the Na+ channel and Na+/Ca2+ exchange. Both series of compds. caused relaxation in isolated rings of dog coronary artery (EC50 values, 1-10 μM), presumably due to release of endothelium-derived relaxing factor (EDRF), since removal of endothelium greatly attenuated the response. Amiloride (1-100 μM) had little effect on either endothelium-intact or denuded arteries. The guanidino-substituted analogs also appeared to block selectively the relaxation response to acetylcholine in the coronary artery, independently of their EDRF-releasing activity. It is proposed that endothelial cells have an active Na+/Ca2+ exchange operating in the forward mode to extrude Ca2+. This mechanism may be important in the control of EDRF release. Furthermore it may be possible to use selective amiloride analog clin. as antihypertensive drugs to relieve spasm in certain arteries such as the coronary and cerebral.

IT *117241-67-5*
RL: BIOL (Biological study)
(endothelium-dependent relaxation in coronary artery induction by, sodium/calcium exchange in, structure in relation to)

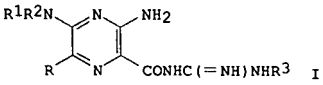
RN 117241-67-5 CAPLUS
CN Pyrazinecarboxamide, 3,5-diamino-6-chloro-N-[imino[(4-pyridinylmethyl)amino]methyl]- (9CI) (CA INDEX NAME)



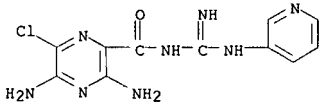
L4 ANSWER 7 OF 20 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 1981:121602 CAPLUS
DOCUMENT NUMBER: 94:121602
TITLE: Heterocyclic-substituted pyrazinoylguanidines, and a pharmaceutical composition containing them
INVENTOR(S): Cragoe, Edward J., Jr.; Woltersdorf, Otto W., Jr.; De Solms, Susan Jane
PATENT ASSIGNEE(S): Merck and Co., Inc., USA
SOURCE: Eur. Pat. Appl., 41 pp.
CODEN: EPXXDW
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
EP 17152	A1	19801015	EP 1980-101589	19800326
EP 17152	B1	19830126		
R: AT, BE, CH, DE, FR, GB, IT, LU, NL, SE				
US 4246406	A	19810120	US 1979-24293	19790327
AU 8056536	A1	19801002	AU 1980-56536	19800318
AU 533298	B2	19831117		
ZA 8001770	A	19811125	ZA 1980-1770	19800325
DK 8001291	A	19800928	DK 1980-1291	19800326
NO 8000878	A	19800929	NO 1980-878	19800326
NO 152560	B	19850708		
NO 152560	C	19851016		
AT 2323	E	19830215	AT 1980-101589	19800326
JP 56158771	A2	19811207	JP 1981-38040	19810318
PRIORITY APPLN. INFO.:			US 1979-24293 A	19790327
			EP 1980-101589 A	19800326

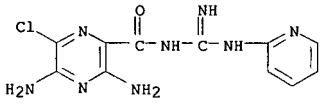
OTHER SOURCE(S): MARPAT 94:121602
GI



AB Diuretic (no data) pyrazinoylguanidines I (R = halogen; R1, R2 = H, alkyl; R3 = heterocyclic) were prepared Thus, Me 3-amino-5-isopropylamino-6-pyrazinecarboxylate was treated with H2NCN and the resulting cyanamide was treated with H2S and methylated to give the isothiourea, which was treated with 2-aminothiazoline to give I (R = Cl, R1 = CHMe2, R2 = H, R3 = 2-thiazolin-2-yl).
IT *76942-93-3P 76942-99-9P*
RL: SPN (Synthetic preparation); PREP (Preparation)
(preparation of)
RN 76942-93-3 CAPLUS
CN Pyrazinecarboxamide, 3,5-diamino-6-chloro-N-[imino(3-pyridinylamino)methyl]- (9CI) (CA INDEX NAME)



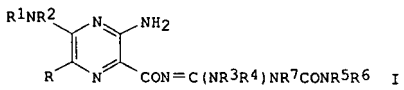
RN 76942-99-9 CAPLUS
CN Pyrazinecarboxamide, 3,5-diamino-6-chloro-N-[imino(2-pyridinylamino)methyl]- (9CI) (CA INDEX NAME)



L4 ANSWER 8 OF 20 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 1978:509585 CAPLUS
DOCUMENT NUMBER: 89:109585
TITLE: Pyrazinecarboxamides
INVENTOR(S): Cragoe, Edward J., Jr.; Woltersdorf, Otto W., Jr.; Habecker, Charles N.
PATENT ASSIGNEE(S): Merck and Co., Inc., USA
SOURCE: U.S., 15 pp.
CODEN: USXXAM
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 4085211	A	19780418	US 1976-722442	19760913
DK 7605314	A	19770616	DK 1976-5314	19761125
SE 7613289	A	19770616	SE 1976-13289	19761126
SE 431452	B	19840206		
SE 431452	C	19840517		
NL 7613276	A	19770617	NL 1976-13276	19761129
AU 7620181	A1	19780608	AU 1976-20181	19761202
AU 511429	B2	19800821		
ES 454160	A1	19780301	ES 1976-454160	19761210
FR 2335226	A1	19770715	FR 1976-37459	19761213
FR 2335226	B1	19790309		
GB 1527297	A	19781004	GB 1976-51940	19761213
HU 175504	P	19800828	HU 1976-ME2034	19761213
CH 630369	A	19820615	CH 1976-15660	19761213
BE 849379	A1	19770614	BE 1976-173235	19761214
ZA 7607431	A	19780726	ZA 1976-7431	19761214
JP 52106877	A2	19770907	JP 1976-149889	19761215
JP 62038350	B4	19870817		
ES 465742	A1	19781001	ES 1978-465742	19780103
PRIORITY APPLN. INFO.:			US 1975-640803 A2	19751215

OTHER SOURCE(S): MARPAT 89:109585
GI



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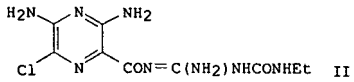


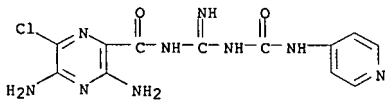
II

AB A series of title amides I (R = halo; R1 = H, alkyl, cycloalkyl, alkenyl; R2 = H, alkyl; NR1R2 = pyrrolidino, piperidino; R3 = H, alkyl, cycloalkyl; R4 = H, alkyl, cycloalkyl; R5 = H, alkyl, cycloalkyl, Ph, substituted phenyl; R6 = H, alkyl, cycloalkyl; NR5R6 = morpholino, piperazino; R7 = H, alkyl; R3R7 = CH2CH2, substituted ethylene) were prepared and are useful as diuretics (no data). Thus, the addition reaction of N-amidino-3,5-diamino-6-chloro-2-pyrazinecarboxamide with EtNCO gave II.

IT *64077-95-8P*
RL: SPN (Synthetic preparation); PREP (Preparation)
(preparation of)

RN 64077-95-8 CAPLUS

CN Pyrazinecarboxamide, 3,5-diamino-6-chloro-N-[imino[[(4-pyridinylamino)carbonyl]amino]methyl]- (9CI) (CA INDEX NAME)



L4 ANSWER 9 OF 20 CAPLUS COPYRIGHT 2006 ACS on STN

ACCESSION NUMBER: 1977:517906 CAPLUS

DOCUMENT NUMBER: 87:117906

TITLE: Pyrazinecarboxamides

INVENTOR(S): Cragoe, Edward Jethro, Jr.; Woltersdorf, Otto William, Jr.; Habecker, Charles Newcomer

PATENT ASSIGNEE(S): Merck and Co., Inc., USA

SOURCE: Ger. Offen., 71 pp.
CODEN: GWXXBX

DOCUMENT TYPE: Patent

LANGUAGE: German

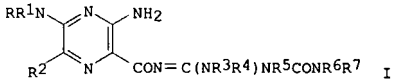
FAMILY ACC. NUM. COUNT: 2

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
DE 2656374	A1	19770616	DE 1976-2656374	19761213
DE 2656374	C2	19890810		
DK 7605314	A	19770616	DK 1976-5314	19761125
SE 7613289	A	19770616	SE 1976-13289	19761126
SE 431452	B	19840206		
SE 431452	C	19840517		
NL 7613276	A	19770617	NL 1976-13276	19761129
AU 7620181	A1	19780608	AU 1976-20181	19761202
AU 511429	B2	19800821		
ES 454160	A1	19780301	ES 1976-454160	19761210
FR 2335226	A1	19770715	FR 1976-37459	19761213
FR 2335226	B1	19790309		
GB 1527297	A	19781004	GB 1976-51940	19761213
HU 175504	P	19800828	HU 1976-ME2034	19761213
CH 630369	A	19820615	CH 1976-15660	19761213
BE 849379	A1	19770614	BE 1976-173235	19761214
ZA 7607431	A	19780726	ZA 1976-7431	19761214
JP 52106877	A2	19770907	JP 1976-149889	19761215
JP 62038350	B4	19870817		
ES 465742	A1	19781001	ES 1978-465742	19780103

PRIORITY APPLN. INFO.: US 1975-640803 A 19751215

GI



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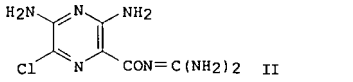


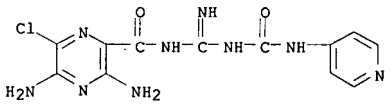
II

AB Diuretic (no data) pyrazinecarboxamides I (R, R1, R3, R4, R5, R7 = H, alkyl; R2 = halo; R6 = H, alkyl, aryl) (>60 compds.) were prepared Thus II was treated with PrNCO to give I (R, R1, R3, R4, R5, R7 = H, R2 = Cl, R6 = Pr).

IT *64077-95-8P*
RL: SPN (Synthetic preparation); PREP (Preparation)
(preparation of)

RN 64077-95-8 CAPLUS

CN Pyrazinecarboxamide, 3,5-diamino-6-chloro-N-[imino[[(4-pyridinylamino)carbonyl]amino]methyl]- (9CI) (CA INDEX NAME)



L4 ANSWER 10 OF 20 CAPLUS COPYRIGHT 2006 ACS on STN

ACCESSION NUMBER: 1971:420438 CAPLUS

DOCUMENT NUMBER: 75:20438

TITLE: N-substituted 3,5-diamino-6-halopyrazinamides

INVENTOR(S): Shepard, Kenneth L.; Cragoe, Edward J., Jr.

PATENT ASSIGNEE(S): Merck and Co., Inc.

SOURCE: U.S., 10 pp.
CODEN: USXXAM

DOCUMENT TYPE: Patent

LANGUAGE: English

FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 3573306	A	19710330	US 1969-804663	19690305

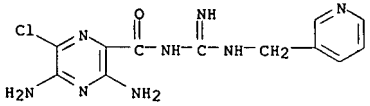
	NL 7001141	A	19700908	NL 1970-1141		19700127
	BE 746816	A	19700904	BE 1970-746816		19700304
PRIORITY APPLN. INFO.:				US 1969-804663	A	19690305

AB Addition of diphenylcarbamoyl chloride to 3,5-diamino-6-chloropyrazinoic acid and Et3N in HCONMe2 gave 3,5-diamino-6-chloropyrazinecarboxylic diphenylcarbamic anhydride (I). Refluxing Na in iso-PrOH with guanidine-HCl and addition of I gave 1-(3,5-diamino-6-chloropyrazinoyl)guanidine. Similarly prepared were 1,1,3,3-tetramethyl-2-(3,5-diamino-6-chloropyrazinoyl)guanidine, 1-(3,5-diamino-6-chloropyrazinoyl)-3-cyanoguanidine, N-methyl-N-(cyanomethyl)-3,5-diamino-6-chloropyrazinecarboxamide, N-(2,2-diethoxyethyl)-3,5-diamino-6-chloropyrazinecarboxamide, N-(2-morpholinoethyl)-3,5-diamino-6-chloropyrazinecarboxamide, N-(4-pyridylmethyl)-3,5-diamino-6-chloropyrazinecarboxamide, N-(2-pyridyl)-3,5-diamino-6-chloropyrazinecarboxamide, 3,5-diamino-6-chloropyrazinecarboxylic acid 1,2-dimethylhydrazide, 3,5-diamino-6-chloropyrazinecarboxylic acid 1-methyl-2-benzylidenehydrazide, and N-(3,5-diamino-6-chloropyrazinoyl)morpholine. These compds. had diuretic activity at 10-100 mg.

IT *14229-20-0P*
RL: SPN (Synthetic preparation); PREP (Preparation)
(preparation of)

RN 14229-20-0 CAPLUS

CN Pyrazinecarboxamide, 3,5-diamino-6-chloro-N-[imino[(3-pyridinylmethyl)amino]methyl]-, dihydrochloride (9CI) (CA INDEX NAME)



●2 HCl

L4 ANSWER 11 OF 20 CAPLUS COPYRIGHT 2006 ACS on STN

ACCESSION NUMBER:	1971:42387 CAPLUS
DOCUMENT NUMBER:	74:42387
TITLE:	Diuretic and natriuretic pyrazinoylguanidines from pyrazinoylureas
INVENTOR(S):	Tull, Roger J.; Pollak, Peter I.
PATENT ASSIGNEE(S):	Merck and Co., Inc.
SOURCE:	U.S., 4 pp. CODEN: USXXAM
DOCUMENT TYPE:	Patent
LANGUAGE:	English
FAMILY ACC. NUM. COUNT:	1
PATENT INFORMATION:	

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 3539569	A	19701110	US 1968-754451	19680821
NL 6910945	A	19700224	NL 1969-10945	19690716
PRIORITY APPLN. INFO.:			US 1968-754451 A	19680821

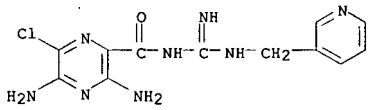
GI For diagram(s), see printed CA Issue.

AB The title process describes the preparation of pyrazinoylguanidines (I) by treatment of the corresponding pyrazinoylureas (II) with a guanidine in a polar nonhydroxylic solvent 5-12 hr at 50-100°, treatment of the mixture with excess dilute mineral acid to precipitate I as the acid addition salt which may be converted to I by conventional procedures. II are obtained from the pyrazinoic acid ester (III, X = OR') by refluxing with NaHNCN and converting the pyrazinoylcyanamide III (X = NHCN) to II by treatment with dilute mineral acid. Thus, H2NCN in MeOH containing Na refluxed 30 min and the solution refluxed 24 hr with III (R1 = R2 = H, X = OMe) gave III (R1 = R2 = H, X = NHCN) (IV), m. >330°. V in DMF stirred (N atmospheric) 8 hr at 70° with H2NC(:NH)NH2.HCl and NaOMe and treated at 40° with 1.5N HCl gave I (R1 = R2 = H, X = Cl), m. 240.5-1.5°. An addnl. 30 compds. obtained by slight modifications of the process are reported.

IT *14229-20-0P*
RL: SPN (Synthetic preparation); PREP (Preparation)
(preparation of)

RN 14229-20-0 CAPLUS

CN Pyrazinecarboxamide, 3,5-diamino-6-chloro-N-[imino[(3-pyridinylmethyl)amino]methyl]-, dihydrochloride (9CI) (CA INDEX NAME)



●2 HCl

L4 ANSWER 12 OF 20 CAPLUS COPYRIGHT 2006 ACS on STN

ACCESSION NUMBER:	1970:43731 CAPLUS
DOCUMENT NUMBER:	72:43731
TITLE:	Diuretic and natriuretic pyrazinoylguanidines
INVENTOR(S):	Cragoe, Edward J., Jr.; Jones, James Holden
PATENT ASSIGNEE(S):	Merck and Co., Inc.
SOURCE:	Fr., 22 pp. CODEN: FRXXAK
DOCUMENT TYPE:	Patent
LANGUAGE:	French
FAMILY ACC. NUM. COUNT:	1
PATENT INFORMATION:	

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
FR 1559541		19690307	FR	19680412
DE 1770174			DE	
GB 1185408			GB	
US 3527758		19700908	US	19670413
ZA 6802332		19680000	ZA	
PRIORITY APPLN. INFO.:			US	19670413

AB Pyrazinoylguanidines, useful as diuretic and natriuretic agents for reducing the excretion of K ions are prepared by treating a pyrazinoic acid azide with a guanidine. Thus, to a solution of 10 g methyl 3-amino-5-diethylamino-6-chloropyrazinoa te in 250 ml EtOH, 20 ml 64% aqueous N2H3 is added and the mixture refluxed 4 hr to give 9 g (87%) 3-amino-5-diethylamino-6-chloropyrazinoic acid hydrazide m. 142-5° (2-propanol). The following I were prepared (R, R1, and m.p. given): EtNH, Cl, 168-70°; CH2:CHCH2NH, Cl, 158-60°; Me2N, Me, -; EtNMe, Cl, 134-6°; Me2N, Cl, 132-4°; p-ClC6H4CH2NH, Cl, 158-60°; Ph, Me, -; MeNH, Cl, 257-60°; BuNH, Cl, 162-5°; PrNH, Cl, 171-3°; HOCH2CH2NH, Cl, 184-5°; C6H13, Cl, -; cyclopentylamino, Cl, 143-5°; Me2NCH2CH2NH, Cl, 161-3°; MeS, Cl, 240-2°; HS, Cl, 218-20°; cyclopropyl-methylamino, Cl, -; HO, Cl, >30°; PrS, Cl,

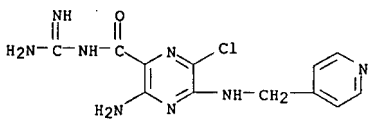
166-8°; Me, Br, 202-5°; cyclopropylamino, Cl, -;
p-MeC6H4CH2NH, Cl, -; p-ClC6H4NH, Cl, -; PhCH2CH2NH, Cl, -; Me2N, Ph,
153-4°; CF3CH2NH, Cl, -; 4-pyridylmethylamino, Cl, -;
furfurylamino, Cl, -; EtS, Cl, 196-9°; n-C5H11S, Cl, 265-7°
(HCl); Me(CH2CH:CH2)N, Cl, -; pyrrolidino, Cl, -; MeN-Pr, Cl,
133-6°; PhCH2S, Cl, -; H, Br, -. A solution of 3.45 g NaNO2 in 20 ml
H2O was added to a solution of 10 g 3,5 -diamino-6-chloropyrazinoic acid
hydrazide in 350 ml 0.5N HCl at 50-5° during 45 min to give 6.4 g
3,5-diamino-6-chloropyrazinoic acid azide (II), m. 160° (explodes).
To a solution of 0.46 g Na in 50 ml 2-propanol, 2 g guanidine-HCl was added,
the mixture cooled, NaCl separated by filtration, 1.07 g II added to the
filtrate the mixture refluxed 30 min., worked up and treated with HCl to
give 0.4 g (3,5-diamino-6-chloropyrazinoyl)guanidine-HCl.2H2O, m.
285-8°; free base m. 240.5-1.5°. The following III (R2 = R3
= R4 = H) were prepared (R, R1 and m.p. given): Et2N, Cl, 215°;
EtNH, Cl, 217-18°; CH2CHCH2NH, cl, 213-14°; Me2N, Me,
262°; MeNEt, Cl, 229-30°; iso-PrNH, Cl, 215°;
p-ClC6H4-CH2NH, Cl, 225-6°; Ph, Me, -; MeNH, Cl, 238-9°;
BuNH, Cl, 219.5°; PrNH, Cl, 221-2°; HO(CH2)2NH, Cl,
272-3°; n-C6H13, Cl, -; cyclopentylamino, Cl, 219-20°;
Me2N(CH2)2NH, Cl, 192.5-4.5°; MeS, Cl, 234.5-6.5°; HS, Cl,
236.5°; cyclo-propylmethylamino, Cl, 220.0-1.5°; HO, Cl,
<310°; PrS, Cl, -; Me, Br, 288°; cyclopropylmethylamino, Cl,
213-15°; p-MeC6H4CH2NH, Cl, 216-17°; p-ClC6H4NH, Cl,
276-8°; Ph-(CH2)2NH, Cl 199-202°; Me2N, Ph, 205-6°;
CF3CH2NH, Cl, 232-3°; 4-pyridylmethylamino, Cl, 239-40°;
furfurylamino, Cl, 217-18°; EtS, Cl, -; n-C5H11S, Cl, -;
Me(CH2CH:CH2)-N, Cl, 207-8°; pyrrolidino, Cl, 244.5-5.5°;
MeNPr, Cl, 214-15°; Me2N, Cl, 216-17°. The following III
(R1 = Cl, R2 = H) were prepared (R, R3, R4, and m.p. given): NH2, H,
HOCH2CH2, 228.5-9.5°; NH2, H, Ph, 272°; NH2, H, PhCH2,
215-16°; NH2, H, p-FC6H4CH2, 216.0-19.5°; NH2, H, PhCH(Me),
153-60°; NH2, H, 2-methylnaphthyl, 243.5-5.5°; NH2, H,
3-pyridylmethyl, 280.5-3.5°; NH2, H, p-MeC6H4CH2, 210-12°;
NH2, Me, PhCH2, 274.5°; NH2, H, o-ClC6H4CH2, 220-3°; NH2, H,
p-ClC6H4CH2, 204-6°; NH2, H, p-MeOCH4CH2, 175.5-9.6°; NH2,
H, 1,3-Me2C6H3CH2, 267.5-70.5°; NH2, H, 3,4-Cl2C6H3-CH2,
216-19°; NH2, H, Ph(CH2)2, 219.0-21.5°; NH2, Me, Me,
275°; NH2, Et, Et, 265°; NH2, Bu, Bu, 148-9°; NH2
(R3R4 =) (CH2)4, -; NH2, (R3R4 =) (CH2)2O(CH2)3, -; Me2CHNH2, Me, Me,
238.5-40.5°; CH2:CHCH2, Me, Me, 213-15°; BuNH, Me, Me,
187.5°; cyclopropylmethylamino, Me, Me, 196-7°; Me2N, Me,
Me, 219°; MeNEt, Me, Me, 217-18°; Et2N, Me, Me,
212-14°. Also prepared was III (R = R2 = R3 = R4 = H, R1 = Br) and
III (R = NH2, R1 = Cl, R2 = R3 = Me, and R4 = H).

IT *1233-60-9P 1634-14-6P*

RL: SPN (Synthetic preparation); PREP (Preparation)
(preparation of)

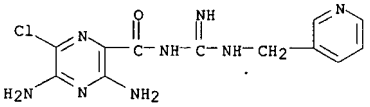
RN 1233-60-9 CAPLUS

CN Pyrazinecarboxamide, N-amidino-3-amino-6-chloro-5-[(4-pyridylmethyl)amino]-
(7CI, 8CI) (CA INDEX NAME)



RN 1634-14-6 CAPLUS

CN Pyrazinecarboxamide, 3,5-diamino-6-chloro-N-[(3-pyridylmethyl)amidino]-
(7CI, 8CI) (CA INDEX NAME)



L4 ANSWER 13 OF 20 CAPLUS COPYRIGHT 2006 ACS on STN

ACCESSION NUMBER: 1969:512983 CAPLUS

DOCUMENT NUMBER: 71:112983

TITLE: (3,5-Diamino-6-halopyrazinoyl) guanidines

INVENTOR(S): Pollak, Peter I.; Tull, Roger J.

PATENT ASSIGNEE(S): Merck and Co., Inc.

SOURCE: Fr., 8 pp.
CODEN: FRXXAK

DOCUMENT TYPE: Patent

LANGUAGE: French

FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
FR 1525692		19680517	FR 1967-109143	19670605
GB 1180785			GB	
US 3472847		19691014	US	19660825
ZA 6703250		19670000	ZA	
PRIORITY APPLN. INFO.:			US	19660825

GI For diagram(s), see printed CA Issue.

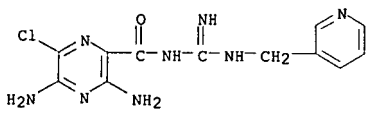
AB The title compds. (I) are prepared by reacting a 3,5-diamino-6-halopyrazinoylcyanamide (II) with NH3 or an amine and are useful as diuretics. Thus, 1 mole methyl 6-chloro-3,5-diaminopyrazinecarboxylate in MeOH is treated with 1 mole sodium cyanamide and refluxed 3 hrs., the solvent evaporated and the residue dissolved in 1 l. concentrated NH4OH containing 3 moles NH4Cl and heated 3 hrs. (pH = 8), to yield I (R1 = R2 = R3 = R4 = H, R = Cl), m. 240.5-1.56° (decomposition); HCl salt m. 293.5°. Similarly was prepared the following I (R = Cl, R1 = R2 = R4 = H) (R3 and m.p. given): Me, 252-4°; CH2CH2OH, - (HCl salt m. 228.5-9.5°); benzyl, 215-16°; o-ClC6H4CH2, 220-3°; p-FC6H4CH2, 216-19.5°; p-MeC6H4CH2, 210-12°; p-MeOC6H4CH2, 175.5-9.5°; 2,4-Me2C6H3CH2, 220-2°; Ph-CHMe, 152-60°; PhCH2CH2, 219-21.5; 3-pyridylmethyl, - (2HCl salt m. 280.5-3.5°. Also the following I (R = Cl, R1 = Me, R3 = R4 = H) (R2 and m.p. given); Me, 216-17°; Et, 229-30°; Pr, 214-15°; iso-Pr, 207-8°. Also I (R = Cl, R1 = H, R3 = R4 = Me (same data given): H, - (HCl.H2O m. 277°); iso-Pr, 238.5-40°; allyl, 213-15°; Bu, 187-5°. Also I (R = Cl, R1 = R4 = H) (R2, R3, and m.p. given): iso-Pr, Me, 300°; iso-Pr, CH2CH2OH, - (HCl semihydrate 185-6°); iso-Pr, PhCH2, 200.5-4.5°; allyl, H, 213-14°; cyclopropylmethyl, H, 220-1.5°. Also the following I (R, R1, R2, R3, R4, and m.p. given); Cl, iso-Pr, H, Me, Me, 238.5-40°; Br, H, H, H, H, 232.5-5.5°; Cl, H, H, Et, Et, 265°; Cl, H, H, Me, PhCH2, - (HCl salt m. 274.5°); Cl, Me, iso-Pr, Me, Me, 209-11°; Cl, Et, Et, Me, Me, 212-14°.

IT *14229-20-0P*

RL: SPN (Synthetic preparation); PREP (Preparation)
(preparation of)

RN 14229-20-0 CAPLUS

CN Pyrazinecarboxamide, 3,5-diamino-6-chloro-N-[imino[(3-pyridinylmethyl)amino]methyl]-, dihydrochloride (9CI) (CA INDEX NAME)



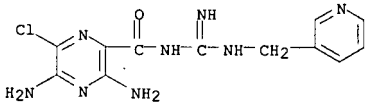
●2 HCl

L4 ANSWER 14 OF 20 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 1969:491530 CAPLUS
DOCUMENT NUMBER: 71:91530
TITLE: (3,5-Diamino-6-halopyrazinoyl)guanidines
INVENTOR(S): Pollak, Peter I.; Tull, Roger J.
PATENT ASSIGNEE(S): Merck and Co., Inc.
SOURCE: Fr., 9 pp.
CODEN: FRXXAK
DOCUMENT TYPE: Patent
LANGUAGE: French
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
FR 1528217		19680607	FR 1967-109146	19670605
GB 1173451			GB	
US 3503972		19700331	US	19681104
ZA 6703247		19670000	ZA	
PRIORITY APPLN. INFO.:			US	19660825

GI For diagram(s), see printed CA Issue.
AB I compds. are prepared Thus, Me 3,5-diamino-6-chloropyrazinoate is converted to 3,5-diamino-6-chloropyrazinamide which is dehydrated to II (R = CN) (III), m. 295°. III (1 mole) is treated with 1.1 moles EtOH and 1.1 moles HCl at 0° to give II [R = C(OEt):NH]-HCl which is heated with EtOH to give II [R = C(OEt)3] (IV). A mixture of 1 mole IV, 1 mole guanidine, and 2 moles Ac2O is heated 1 hr. at 140° to give II [R = C(OEt):NC(:NH)NH2] which is heated 5 hrs. with 2N HCl to give (3,5-diamino-6-chloropyrazinoyl)guanidine-HCl, m. 293.5° (decomposition) Similarly prepared are the following I (n = 0, R4 = H) [R, R1, R2, R3, and m.p. (decomposition) given]: H, H, Me, H 252-4°; H, H, Me, Me, - (HCl salt monohydrate m. 277°); H, H, Et, Et, 265°; H, H, Me, PhCH2, - (HCl salt m. 274.5°); H, H, CH2CH2OH, H, - (HCl salt m. 228.5-9.5°); H, H, PhCH2, H, 215-16°; H, H, m-ClC6H4CH2, H, 220-3°; H, H, p-FC6H4CH2, H, 216-19.5°; H, H, p-MeC6H4CH2, H, 210-12°; H, H, p-MeOC6H4CH2, H, 175.5-9.5°; H, H, 3,4-Me2C6H3CH2, H, 220-2°; H, H, PhCHMe, H, 152-60°; H, H, PhCH2CH2, H, 219-21.5°; H, H, 3-pyridylmethyl, H, - (2HCl salt m. 280.5-3.5°); H, iso-Pr, Me, H, >300°; H, iso-Pr, Me, Me, 238.5-40°; H, iso-Pr, CH2CH2OH, H, - (HCl salt hemihydrate m. 185-6°); H, iso-Pr, PhCH2, H, 200.5-4.5°; H, allyl, H, H, 213-14°; H, allyl, Me, Me, 213-15°; H, Bu, Me, Me, 187.5°; H, cyclopropyl, H, H, 220-1.5°; Me, Me, H, H, 216-17°; Me, Et, H, H, 229-30°; Me, Pr, H, H, 214-15°; Me, iso-Pr, H, H, 207-8°; Me, iso-Pr, Me, Me, 209-11°; Et, Et, Me, Me, 212-14°; (3,5-diamino-6-pyrazinamido)guanidine-HCl, m. 281-2° (decomposition); I (n = 1, R = R1 = Me, R2 = R3 = R4 = H), m. 221° (decomposition); I (n = 1, R = R1 = R4 = H, R2 = R3 = Me)-HCl, m. 279-80° (decomposition); (3,5-diamino-6-bromopyrazinoyl)guanidine, m. 232.5-5.5°; I [n = 0, R = R1 = R2 = H, (R3R4 =) CH2CH2], m. 222.5-3.5°.

IT *14229-20-0P*
RL: SPN (Synthetic preparation); PREP (Preparation)
(preparation of)
RN 14229-20-0 CAPLUS
CN Pyrazinecarboxamide, 3,5-diamino-6-chloro-N-[imino[(3-pyridinylmethyl)amino]methyl]-, dihydrochloride (9CI) (CA INDEX NAME)



●2 HCl

L4 ANSWER 15 OF 20 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 1969:481411 CAPLUS
DOCUMENT NUMBER: 71:81411
TITLE: (3,5-Diamino-6-halopyrazinoyl and -pyrazinamido)guanidines
INVENTOR(S): Pollak, Peter I.; Tull, Roger J.
PATENT ASSIGNEE(S): Merck and Co., Inc.
SOURCE: Fr., 6 pp.
CODEN: FRXXAK
DOCUMENT TYPE: Patent
LANGUAGE: French
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
FR 1525671		19680517	FR 1967-109099	19670605
GB 1158399			GB	
ZA 6703261		19670000	ZA	
PRIORITY APPLN. INFO.:			US	19660825

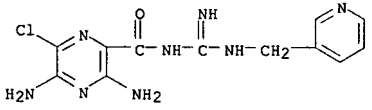
GI For diagram(s), see printed CA Issue.
AB Pyrazinoic acids are treated with guanidines h2N(NH)nC(:NR)NR1R2 to give compds. I. A mixture of 1 mole 6-chloro-3,5-diaminopyrazinoic acid, 3 moles guanidine, and 500 ml. BuOH is refluxed 8 hrs. to give (3,5-diamino-6-chloropyrazinoyl)guanidine, m. 240-1.50° (decomposition). Similarly prepared are the following I (X = Cl, n = O, R = H) (R1, R2, R3, R4, and decomposition temperature given): Me, H, H, H, 252-4°; Me, Me, H, H, -, HCl salt monohydrate decompose 277°; Et, Et, H, H, 265°; Me, PhCH2, H, H, -, HCl salt decompose 274.5°; CH2CH2OH, H, H, H, HCl salt m. 228.5-9.5°; PhCH2, H, H, H, 215-16°; o-ClC6H4CH2, H, H, H, 220-3°; p-FC6H4CH2, H, H, H, 216-19.5; p-MeC6H4CH2, H, H, H, 210-12°; p-MeOC6H4CH2, H, H, H, 175.5-9.5°; 2,4-Me2C6H3CH2, H, H, H, 220-2°; PhCHMe, H, H, H, 152-60°; PhCH2CH2, H, H, H, 219-21.5°; 3-pyridylmethyl, H, H, H, -, 2HCl salt decompose 280-3.5°; Me, H, H, iso-Pr, >300°; Me, Me, H, iso-Pr, 238.5-40°; CH2CH2OH, H, H, iso-Pr, -, HCl salt hemihydrate decompose 185-6°; PhCH2, H, H, iso-Pr, 200.5-4.5; H, H, H, allyl, 213-14°; Me, Me, H, allyl, 213-15°; Me, Me, H, Bu, 187.5°; H, H, H, cyclopropylmethyl, 220-1.5°; H, H, Me, Me, 216-17°; H, H, Me, Et, 229-30°; H, H, Me, Pr [sic], 214-15°; H, H, Me, iso-Pr, 207-8°; Me, Me, Me, iso-Pr, 209-11°; Me, Me, Et, Et, 212-14°; and the following compds. (decomposition temperature given): I (X = Cl, n = 1, R = R1 = R2 = R3 = R4 = H)-HCl,

281-2°; I (X = Cl, n = 1, R = R1 = R2 = H, R3 = R4 = Me), 221°; I (X = Cl, n = 1, R = R3 = R4 = H, R1 = R2 = Me)-HCl, 279-80°; I (X = Br, n = 0, R = R1 = R2 = R3 = R4 = H), 232.5-5.5°; I [X = Cl, n = O, (RR2N =) ethyleneimino, R1 = R3 = R4 = H = H] [sic], 222.5-3.5°.

IT *14229-20-0P*
RL: SPN (Synthetic preparation); PREP (Preparation)
(preparation of)

RN 14229-20-0 CAPLUS

CN Pyrazinecarboxamide, 3,5-diamino-6-chloro-N-[imino[(3-pyridinylmethyl)amino]methyl]-, dihydrochloride (9CI) (CA INDEX NAME)



●2 HCl

L4 ANSWER 16 OF 20 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 1969:96820 CAPLUS
DOCUMENT NUMBER: 70:96820
TITLE: Pyrazinoylguanidine and pyrazinamidoguanidine
INVENTOR(S): Pollak, Peter I.; Tull, Roger J.
PATENT ASSIGNEE(S): Merck and Co., Inc.
SOURCE: U.S., 4 pp.
CODEN: USXXAM
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 3432502	A	19690311	US 1966-574909	19660825
NL 6707563	A	19680226	NL 1967-7563	19670531
DK 115771	B	19691110	DK 1967-2864	19670601
BE 699435	A	19671204	BE 1967-699435	19670602
ES 341321	A1	19681016	ES 1967-341321	19670602
CH 484161	A	19700115	CH 1967-484161	19670607
GB 1184709	A	19700318	GB 1967-1184709	19670607

PRIORITY APPLN. INFO.: US 1966-574909 A 19660825

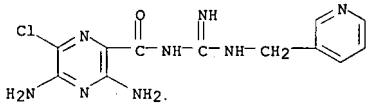
GI For diagram(s), see printed CA Issue.

AB (3,5-Diamino-6-halopyrazinoyl)guanidine and (3,5-diamino-6-halopyrazinamido)guanidine, possessing diuretic and saluretic properties without enhancing K excretion, are prepared by treating 3,5-diamino-6-halopyrazinoic acid hydrazide with a guanidine or an aminoguanidine. Thus, 1 mole 6-choro-3,5-diaminopyrazinoic acid hydrazide and 3 moles chloral were heated 2 hrs. at 80° in 300 ml. dimethoxyethane. The solution was then cooled to room temperature and 1 mole guanidine added with stirring. The mixture was heated an addnl. 2 hrs. at 80° removing most of the solvent by distillation and the product (6-chloro-3,5-diaminopyrazinoyl)guanidine was precipitated by addition of 300 ml. N HCl yielding the HCl salt, m. 293.5° (decompose). Similarly prepared were I (n, R, R1, R2, R3, R4, R5, and m.p. given): 0, Br, H, H, H, H, H, 232.5-35.5°; 0, Cl, H, H, Me, H, H, 252-4°; 0, Cl, H, H, Me, Me, H, HCl monohydrate 277°; 0, Cl, H, H, Et, Et, H, 265°; 0, Cl, H, H, Me, CH2Ph, H, HCl 274.5°; 0, Cl, H, H, CH2CH2OH, H, H, HCl 228.5-9.5°; 0, Cl, H, H, CH2Ph, H, H, 215-16°; 0, Cl, H, H, 2-ClC6H4CH2, H, H, 220-3°; 0, Cl, H, H, 4-FC6H4CH2, H, H, 216-19.5°; 0, Cl, H, H, 4-MeC6H4CH2, H, H, 210-22°; 0, Cl, H, H, 4-MeOC6H4CH2, H, H, 175.5-9.5°; 0, Cl, H, H, 2,4-Me2C6H3CH2, H, H, 220-2°; 0, Cl, H, H, PhMeCH, H, H, 152-60°; 0, Cl, H, H, PhCH2CH2, H, H, 219-21.5°; 0, Cl, H, H, 3-pyridylmethyl, H, H, 2HCl 280.5-83.5°; 0, Cl, H, H, H, (R4R5 =) CH2CH2, 222.5-3.5°; 0, Cl, H, iso-Pr, Me, H, H, >300°; 0, Cl, H, iso-Pr, Me, Me, H, 238.5-40°; 0, Cl, H, iso-Pr, CH2CH2OH, H, H, HCl hemihydrate 185-6°; 0, Cl, H, iso-Pr, CH2Ph, H, H, 200.5-4.5°; 0, Cl, H, CH2CH:CH2, H, H, H, 213-14°; 0, Cl, H, CH2CH:CH2, Me, Me, H, 213-15°; 0, Cl, H, Bu, Me, Me, H, 187.5°; 0, Cl, H, cyclopropylmethyl, H, H, H, 220-1.5°; 0, Cl, Me, Me, H, H, H, 216-17°; 0, Cl, Me, Et, H, H, H, 229-30°; 0, Cl, Me, Pr, H, H, H, 214-15°; 0, Cl, Me, iso-Pr, H, H, H, 207-8°; 0, Cl, Me, iso-Pr, Me, Me, H, 209-11°; 0, Cl, Et, Et, Me, Me, H, 212-14°; 1, Cl, H, H, H, H, H, 281-2° (decompose); 1, Cl, Me, Me, H, H, H, 221° (decompose); 1, Cl, H, H, H, (R4R5 =) CH2CH2, 249-51°; 1, Cl, H, H, H, H, H, HCl 279-80° (decompose).

IT *14229-20-0P*
RL: SPN (Synthetic preparation); PREP (Preparation)
(preparation of)

RN 14229-20-0 CAPLUS

CN Pyrazinecarboxamide, 3,5-diamino-6-chloro-N-[imino[(3-pyridinylmethyl)amino]methyl]-, dihydrochloride (9CI) (CA INDEX NAME)



●2 HCl

L4 ANSWER 17 OF 20 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 1968:436172 CAPLUS
DOCUMENT NUMBER: 69:36172
TITLE: (3-Amino-2-pyrazinecarbonyl)guanidines
INVENTOR(S): Cragoe, Edward J., Jr.
PATENT ASSIGNEE(S): Merck and Co., Inc.
SOURCE: U.S., 26 pp.
CODEN: USXXAM
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 3313813		19670411	US 1963-313315	19621030
DE 1795438			DE	

GI For diagram(s), see printed CA Issue.

AB Title compds. I are prepared from II, III, and IV. Thus, 3318 g. SO2Cl2 is added in 30 min. to 765 g. Me 3-amino-2-pyrazinecarboxylate in 5.1 C6H6; the mixture is agitated 1 hr., refluxed 5 hrs., and agitated overnight to give 724 g. Me 3-amino-5,6-dichloropyrazinecarboxylate (V), m. 233-4° (MeCN). A mixture of 100 g. V and 1.1 Me2SO is heated to

65° and NH3 gas is introduced into the mixture in 45 min. at 65-70°; the mixture is cooled to 10° and NH3 is introduced in 1.25 hrs. to give 91.5% Me 3,5-diamino-6-chloropyrazinecarboxylate, m. 212-13° (MeCN). Also prepared, by known methods are the following II (X, Y, Z, and m.p. given): MeO, NH2, H, 252-4° (decomposition); MeO, NH2, Br, 217-19°; MeO, NH2, iodine, 200-2°; MeO, PhNH, Cl, 171.5-73°; MeO, p-ClC6H4NH, Cl, 207-8°; MeO, Me2N, Cl, 145.5-6.5°; MeO, MeS, Cl, 214-16°; MeO, MeSO, Cl, 237.5-40.5° (decomposition); MeO, OH, Cl, .apprx.245° (decomposition); MeO, OH, H, 220-60° (decomposition); MeO, NH2,H, 252-4° (decomposition); MeO, Me2N, H, 242.5-3.5°; MeO, MeO, H, 205.5-7.5°; MeO, PhCH2NH, H, 157-8°; MeO, MeO, MeO, Cl, 255-7°; MeO, MeS, Cl, 212-14°; MeO, SH, Cl, 207-8° (decomposition); MeO,EtO, Cl, 123-5°; MeO, H, Me, 138.5-40.5°; MeO, Cl, Me, 176.5-9.5°; MeO, Me2N, Me, 108.5-10.5°; MeO, Me, H, 165-7°; MeO, Me, Br; 179-81°; NH2, H, Et, 165.5-8.5°; OH, H, Et, 149-52°; MeO, H, Et, 85-7.5°; OH, cyclohexyl, H, 182.5-3.5°; MeO, cyclohexyl, H, 173-4.5°; NH2, H, cyclohexyl, -; OH, H, cyclohexyl, -; MeO, H, cyclohexyl, 126.5-8.0°; NH2, H, cyclopropyl, 185.5-7.5°; OH, H, cyclopropyl, 169-72°; MeO, H, cyclohexyl, 112.5-14.5°; MeO, Ph, H, 231-2°; MeO, H, Ph, 140-1°; MeO, Cl, Ph, 187.5-91.5°; MeO, Ph, Br, 217-21°; OH, H, p-ClC6H4, 213-15°; MeO, H, p-ClC6H4, 181.5-3.5°; MeO, Cl, Ph, 187.5-90.5°; MeO, Me2N, Ph, 167-9.5°; MeO, H, Cl, 142° (decomposition); MeO, MeHN, Cl, 221-2°; MeO, EtNH, Cl, 149-50°; MeO, PrNH, Cl, 138-40°; MeO, iso-PrNH, Cl, 125.5-6.5°; MeO, CH2:CHCH2NH, Cl, 105-6.5°; MeO, BuNH, Cl, 140-2°; MeO, sec-BuNH, Cl, 106-8°; MeO, iso-BuNH, Cl, 113.5-15.5°; MeO, tert-BuNH, Cl, 98-108°; MeO, Me(CH2)4NH, Cl, 100.5-2.5°; MeO, BuCHMeNH, Cl, -; MeO, Et2CHNH, Cl, -; MeO, Me(CH2)5NH, Cl, 72.5-5.5°; MeO, cyclopropylmethylamino, Cl, 132-3°; MeO, cyclopropylamino, Cl, 167-9°; MeO, cyclopentylamino, Cl, 119.5-21.5°; MeO, PhCH2NH, Cl, 157-8°; MeO, p-MeC6H4CH2NH, Cl, 112.5-14.5°; MeO, o-FC6H4CHNH, Cl, 171-4°; MeO, p-ClC6H4CH2NH, Cl, 136-7°; MeO, PhCH2CH2NH, Cl, 115-19°; MeO, F3CCH2NH, Cl, 153-4°; MeO, F3CCH2CH2NH, Cl, 124.5-5.5°; MeO, HOCH2CH2NH, Cl, 155-7°; MeO, HOCH2(CHOH)4CH2NH, Cl, 172-5°; MeO, H2NCH2CH2NH, Cl, 265°; MeO, Me2NCH2CH2NH, Cl, 257°; MeO, 4-pyridylmethylamino, Cl, 95-7°; Me, 2-furylmethylamino, Cl, 148-9°; MeO, MeEtN, Cl, 102-4°; MeO, MePrN, Cl, 83.5-5.5°; MeO, iso-PrMeN, Cl, 75.5-7.5°; MeO, Me(CH2:CHCH2)N, Cl, 90.5-2°; MeO, MeBun, Cl, 59.5-61.5°; MeO, Et2N, Cl, 99-101°; MeO, EtPrN, Cl, -; MeO, iso-PrEtN, Cl, -; MeO, Et(CH2:CHCH2)N, Cl, -; MeO, EtBun, Cl, 77.5-9.5°; Me, Pr2N, Cl, 68.5-71.5°; MeO, PrBuN, Cl, -; MeO, 1-pyrrolidinyl, Cl, 168-71°; MeO, hexamethylenimino, Cl, 109-11°; MeO, 4-methylpiperazino, Cl, 186-8°; MeO, MeNHNH, Cl, 136.5-8°; MeO, Me2NCH2CH2O, Cl, 134.5-6.5°; NH2, H, Cl, 227-30°; OH, H, MeSO2, 239-42° (decomposition).

p-Methylbenzylamine is treated with H2NC(:NH)SMe.0.5H2SO4 to give 28% p-MeC6H4CH2NHC(:NH)NH2HCl, m. 153-5°. Similarly prepared are Me(PhCH2)NC(:NH)NH2.HCl, m. 122.5-5.5°, and the following RNHC(:NH)NH2.HCl (R and m.p. given): o-ClC6H4CH2, 131-6°; p-ClC6H4CH2, 162.5-4.5°; p-MeOC6H4CH2, 132-7°; 2,4-Me2C6H3CH2, 105-15°; 2,4-Cl2C6H3CH2, 145-8°; 3,4-Cl2C6H3CH2, 153-7°; PhCH2CH2, 135-8°; PhCH2, 175-8°. 5,6-Diaminouracil-HCl (17.9 g.) is treated at 60° with 14.9 g. cyclohexylglyoxal-0.5H2O to give 7.5 g. 7-cyclohexyllumazine [III (X = H, Y = cyclohexyl)], m. 229-31°, which is hydrolyzed to give II (X = OH, Y = cyclohexyl, Z = H). Similarly prepared are (m.p. given): III (X = Me, Y = Ph) [or III (X = Me, Y = Me)], 281.5-2.5°; III (X = Ph, Y = Me) [or III (X = Me, Y = Ph) [sic], 254.5-5.5°; II (X = OH, Y = Ph, Z = Me) [or II (X = OH, Y = Me, Z = Ph)], 193.5-4.5°; II (X = OH, Y = Me, Z = Ph) [or II (X = OH, Y = Ph, Z = Me)] [sic], 155-6°. II (X = MeO, Y = Ph, Z = Me) [or II (X = MeO, Y = Me, Z = Ph)] (m. 163-4°) and II (X = MeO, Y = Me, Z = Ph) [or II (X = MeO, Y = Ph, Z = Me)][sic] (m. 162.5-3.5°) are prepared by esterification. Methyl 3-isopropylidenamino-6-anilino-2-pyrazinecarboxylate, m. 195.5-7.5°, is prepared from Me2CO and the amine. Me 3-amino-5,6,7,8-tetrahydroquinoxaline-2-carboxylate, m. 154-5°, and Me 3-amino-7-chloroquinoxaline-2-carboxylate, m. 224.5-5.5°, are prepared by esterification. Alloxan-H2O (61.44 g.) is treated with 60 g. 3,4-(H2N)2C6H3Cl to give 33% 8-chloroalloxazine, m. 365-6°, and 42% 7-Chloroalloxazine, m. >380°, which is treated at 165° with NH3 in an autoclave to give 68% 3-amino-7-chloroquinoxaline-2-carboxylic acid, m. 191-2° (decomposition). A mixture of 33 g. II (X = NH2, Y = H, Z = Cl), 200 ml. Ac2O, and 200 ml. HC(OEt)3 is refluxed 1.5 hrs. to give 20 g. 4-hydroxy-6-chloropteridine (VI), m. 268-70° (decomposition). VI (5.5 g.) is treated with 4.4 g. PhCH2SH to give 5.5 g. 4-hydroxy-6-benzylthiopteridine (VIII), m. 233-5°. Similarly prepared is 4-hydroxy-6-methylthiopteridine, m. 289.5-91.5°. VII is heated with NaOH to give II (X = OH, Y = H, Z = PhCH2S(VIII), m. 138.9°. Similarly prepared is II (X = OH, Y = H, Z = MeS), m. 182-4° (decomposition). II (X = MeO, Y = Me2N, Z = Cl) (11.5 g.) is treated with 26.3 g. H2NC(:NH)NH2.HCl (IX) in the presence of 5.75 g. Na to give 93% (3-amino-5-dimethylamino-6-chloro-2-pyrazinecarbonyl)guanidine (X), m. 216-17°, HCl salt m. 298° (decomposition). Similarly prepared is I.HCl (R = R1 = H, X = Y = Cl) (m. 259-61°) which is treated with Me2NH to give X. II (X = MeO, Y = Me2NCH2CHO, Z = Cl) (9.4 g.) is treated with 20.0 g. IX in the presence of 4 g. Na to give 2.5 g. I.2HCl [R = R1 = H, X = NHC(:NH)NH2, Z = Cl], m. >340°. A solution of 8.5 5. VIII in 50 ml. Ac2O is heated 5 hrs. to give 6.6 g. 2-methyl-6-benzylthio-4H-pyrazine[2,3-d][1,3]oxazin-4-one [IV (X = PhCH2S)] (XI), m. 116.5-18.5°; similarly prepared is IV (X = MeS), m. 189-91°. XI (3.4 g.) is treated with 5.0 g. IX in the presence of 1.0 g. Na to give 1.1 g. I (R = R1 = X = H, Y = PhCH2S), m. 171-3° (decomposition). Also prepared, by the above or related methods, are the following I (R = R1 = H) (X, Y, and m.p. given): NH2, Br, 232.5-5.5° (decomposition); NH2, iodine, 273-4° (decomposition); H, MeS, 203-5°; H, MeSO2, 224-6° (decomposition); OH, H, >310°; NH2, H, 286-8°; Me2N, H, 224-5°; MeO, H, 229-30°; PhCH2NH, H, 231-3°; the following I (R = R1 = H, Y, = Cl) (X and m.p. given): NH2, 240.5-1.5° (HCl salt m. 293.5°); MeNH, 238-9°; EtNH, 217-18°; PrNH, 221-2°; iso-PrNH, 215°; CH2:CHCH2NH, 213-14°; BuNH, 219.5°; sec-BuNH, 208-9°; iso-BuNH, 221°; tert-BuNH, 222-3°; Me(CH2)4NH, 215-16°; BuCHMeNH, 186.5-8.5°; Et2CHNH, 209-11°; Me(CH2)5NH, 194.5-6.5°; cyclopropylmethylamino, 220-1.5°; cyclopropylamino, 213-15°; cyclopentylamino, 219-20°; PhCH2NH, 206-9°; p-MeC6H4CH2NH, 216-17°; o-FC6H4CH2NH, 206-8°; p-ClC6H4CH2NH, 225-6°; PhCH2CH2NH, - (HCl salt m. 199-202°); F3CCH2NH, 232-3°; F3CCH2CH2NH, 221-2.5°; HOCH2CH2NH, - (HCl salt m. 272-3°); HOCH2(CHOH)4CH2NH, 223-4°; H2NCH2CH2NH, - (HCl salt m. 311°); Me2NCH2CH2NH, 192.5-4.5°; 4-pyridylmethylamino, 239-40°; 2-furylmethylamino, 217-18°; PhNH, 246.5-8.5°; p-ClC6H4NH, 276-8°; MeEtN, 229-3°; MeBuN, 214-15°; iso-PrMeN, 207-8°; Me(CH2:CHCH2)N, 207-8°; MeBuN, 208-9°; Et2N, 215°; EtPrN, 224-5°; iso-PrEtN, 207-8°; Et(CH2:CHCH2)N, 208-9°; EtBuN, 200.5-1.5°; Pr2N, 221-2°; PrBuN, 215-17°; 1-pyrrolidinyl, 244.5-5.5°; hexamethylenimino, 224-5°; 4-methylpiperazino, - (2HCl salt m; 229-300°); MeNHNH, 234°; Cl2N, - (HCl salt m. 259-61°); MeNH, 218-19° (decomposition); Me2NNMe, - [2HCl salt m. 262° (decomposition)]; MeNH, 210° (decomposition) [sic]; Me2N, 245° (decomposition); MeBrN, - [HCl salt m. 288° (decomposition)]; EtNH, 207.5-9.5° (decomposition); cyclohexylamino, 221-2° (decomposition); cycloheptylamino, 228-30° (decomposition); cyclopropylamino,

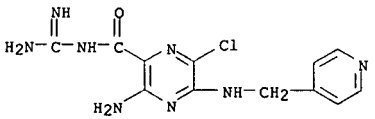
196.5-9° (decomposition); PhNH, 224-6° (decomposition); PhNH, 194.5-5.5° (decomposition)[sic]; Ph2N, 234.5-5.5°; PhClN, 214-16° (decomposition); PhBrN, 234-6° (decomposition); p-ClC6H4NH, 282-5° (decomposition); MePhN, 212-13° (decomposition); MePhN, 218-19° (decomposition)[sic]; Me2NNPh, 204-6° (decomposition); 1-pyrrolidinyl, 220-1°; 1-pyrryl, 211-13°; 3-chloro-1-pyrrolyl, 246-7° (decomposition); (3-isopropylidineamino-6-anilino-2-pyrazinecarbonyl)guanidine, 214-16° (decomposition); (3-acetoamido-6-methylthio-2-pyrazinecarbonyl)guanidine, 220-2°; the following I (X = NH2, Y = Cl) (R, R1, m.p., and m.p. HCl salt given): H, HOCH2CH2, -, 228.5-9.5° (decomposition); H, Ph, -, -, [MeSO3H salt m. 272° (decomposition)]; H, PhCH2, 215-16° (decomposition); -; H, p-FC6H4CH2, 216-19.5° (decomposition), -; H, PhCHMe, 153-60° (decomposition), -; H, 2-C10H7CH2, 243.5-5.5° (decomposition), -; H, 3-pyridylmethyl, 280.5-3.5° (decomposition), -; H, p-MeC6H4CH2, 210-12° (decomposition), -; Me, PhCH2, 274.5° (decomposition), -; H, o-ClC6H4CH2, 220-3° (decomposition), -; H, p-ClC6H4CH2, 204-6° (decomposition), -; H, p-MeOC6H4CH2, 175.5-9.5° (decomposition), -; H, 2,4-Me2C6H3CH2, 220-2° (decomposition), -; H, 2,4-Cl2C6H3CH2, -, 267.5-70.5° (decomposition); H, 3,4-Cl2C6H3CH2, 216-19° (decomposition), -; H, PhClH,CH2, 219-21° (decomposition), -; Me, Me, 240° (decomposition), -, [HCl.H2O salt m. 275° (decomposition)]; H, octahydrol-azocinyl, -, -; Et, Et, 265° (decomposition), -; Bu, Bu, 148-9°, -; (RR1 =) (CH2)4, -, -; (RR1 =) 3-oxapentamethylene, -, -; the following I (R = R1 = Me, Y = Cl) (X and m.p. given): iso-PrNH, 238-40.5°; CH2:CHCH2NH, 213-15°; BuNH, 187.5°; cyclopropylmethylamino, 196-7°; Me2N, 219°; MeEtN, 217-18°; iso-PrMeN, 209-11°; Et2N, 212-14°; I (R = H, R1 = HOCH2CH2, X = iso-PrNH, Y = Cl).HCl.0.5H2O [m. 185-6° (decomposition)], and 1-(3,5-diamino-6-chloro-2-pyrazinecarbonyl)2,3-dimethylguanidine.

IT *1233-60-9P 1634-14-6P*

RL: SPN (Synthetic preparation); PREP (Preparation)
(preparation of)

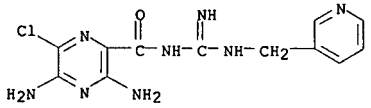
RN 1233-60-9 CAPLUS

CN Pyrazinecarboxamide, N-amidino-3-amino-6-chloro-5-[(4-pyridylmethyl)amino]-(7CI, 8CI) (CA INDEX NAME)



RN 1634-14-6 CAPLUS

CN Pyrazinecarboxamide, 3,5-diamino-6-chloro-N-[(3-pyridylmethyl)amidino]-(7CI, 8CI) (CA INDEX NAME)



L4 ANSWER 18 OF 20 CAPLUS COPYRIGHT 2006 ACS on STN

ACCESSION NUMBER: 1968:49653 CAPLUS

DOCUMENT NUMBER: 68:49653

TITLE: Derivatives of pyrazine

INVENTOR(S): Pollak, Peter I.; Tull, Roger J.

PATENT ASSIGNEE(S): Merck and Co., Inc.

SOURCE: U.S., 4 pp.
CODEN: USXXAM

DOCUMENT TYPE: Patent

LANGUAGE: English

FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 3328404		19670627	US 1966-574904	19660825
FR 1525691			FR	
GB 1173342			GB	
ZA 6703249		19670000	ZA	

GI For diagram(s), see printed CA Issue.

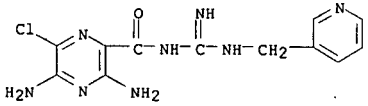
AB (3,5-Diamino-6-halopyrazinoyl)guanidine and (3,5-diamino-6-halopyrazinamido)guanidine compds. of structure I possess diuretic properties and selectively enhance the excretion of Na and Cl and suppress the excretion of K. Thus, 0.1 mole II (R = R1 = R2 = H, R3 = Me) (IIa) heated 12 hrs. at 100° in 200 ml. liquid NH3 gives 90% 3,5-diamino-6-chloropyrazinamide (III), m. 218.5-20.6° (MeOH) (Step A). III (0.0115 mole) in 20 ml. HCONMe2 and 2 ml. POCl3 heated 10 min. at 80° gives 77% 3,5-diamino-6-chloropyrazinonitrile, m. 295° (H2O), which (1 mole) in 1.1 moles absolute EtOH and 500 ml. Et2O is saturated with 1.1 moles HCl gas at 0° and kept 4 days at 0°. The formed Et 3,5-diamino-6-chloropyrazinimidate-HCl is heated 16 hrs. at 40° in 1 l. EtOH with 2 moles HNMe2 to give N,N-dimethyl-3,5-diamino-6-chloropyrazinamidine. This is refluxed 1 hr. with 1 mole guanidine in EtOH, the mixture evaporated, and the residue refluxed 5 hrs. in 500 ml. 2N HCl to give (3,5-diamino-6-chloropyrazinoyl)guanidine-HCl, m. 293.5° (decomposition). (Step B). The 6-bromo analog is prepared similarly the as free base, m. 232.5-5.5°. Replacing guanidine by aminoguanidine in B gives (3,5-diamino-6-chloropyrazinamido)guanidine, m. 281-2° (decomposition). (Step C). Replacing IIa in A by Me 3-amino-5-dimethylamino-6-chloropyrazinoate and following the other steps gives (3-amino-5-dimethylamino-6-chloropyrazinamido)guanidine, m. 221° (decomposition). Replacing aminoguanidine by 1-amino-3,3-dimethylguanidine in C gives 1-(3,5-diamino-6-chloropyrazinamido)-3,3-dimethylguanidine-HCl, m. 279-80° (decomposition). With these methods and using the appropriate Me 3-amino-5-NR1R2-substituted-6-chloropyrazinoate and the appropriate guanidine the following I (R = Cl, R5 = H) are prepared [R1, R2, R3, R4, and m.p. (all with decomposition) given]:

H, H, Me, H, 252-4°; H, H, Me, Me, - (HCl.H2O salt m. 277°); H, H, Et, Et, 265°; H, H, Me, PhCH2, - (HCl salt m. 274.5°); H, H,CH2CH2OH, H, - (HCl salt m. 228.5-9.5°); H, H, PhCH2, H, 215-16°; H, H, o-ClC6H4CH2, H, 220-3°; H, H, p-FC6H4CH2,H, 216-19.5°; H, H, p-MeC6H4CH2, H, 210-12°; H, H, p-MeOC6H4CH2, H, 175.5-9.5°; H, H, 2,5-Me2C6H3CH2, H, 220-2°, H, H, PhCHMe, H, 152-60°; H, H, PhCH2-CH2, H, 219-21.5°; H, H, 3-pyridylmethyl,, -H (di-HCl salt m. 280.5-3.5°); H, H, H, (R4R5) = CH2CH2, 222.5-23°; H, iso-Pr, Me, H, >300°; H, iso-Pr, Me, Me, 238.5-40°; H, iso-Pr, CH2CH2OH, H, -(HCl.0.5H2Osalt m. 185-6°); H, iso-Pr, PhCH2, H, 200.5-4.5°; H, CH2:CHCH2, H, H, 213-14°; H, CH2:CHCH2, Me, Me, 213-15°; H, Bu, Me,Me, 187.5°; H, cyclopropylmethyl, H, H, 220-1.5°; Me, Me, H, H, 216-17°; Me, Et, H, H, 229-30°; Me, Pr, H, H, 214-15°; Me, iso-Pr, H, H, 207-8°; Me, iso-Pr, Me, Me, 209-11°; Et, Et, Me, Me, 212-14°.

IT *14229-20-0P*

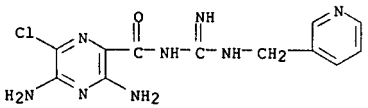
RL: SPN (Synthetic preparation); PREP (Preparation)
(preparation of)

RN 14229-20-0 CAPLUS
CN Pyrazinecarboxamide, 3,5-diamino-6-chloro-N-[imino[(3-pyridinylmethyl)amino]methyl]-, dihydrochloride (9CI) (CA INDEX NAME)



●2 HCl

L4 ANSWER 19 OF 20 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 1967:37887 CAPLUS
DOCUMENT NUMBER: 66:37887
TITLE: Pyrazine diuretics. II. N-amidino-3-amino-5-substituted 6-halopyrazinecarboxamides
AUTHOR(S): Cragoe, Edward J., Jr.; Woltersdorf, Otto W., Jr.; Bicking, John B.; Kwong, Sara F.; Jones, James Holden
CORPORATE SOURCE: Div. of Merck and Co., Inc., Merck Sharp and Dohme Res. Labs., West Point, PA, USA
SOURCE: Journal of Medicinal Chemistry (1967), 10(1), 66-75
CODEN: JMCMAR; ISSN: 0022-2623
DOCUMENT TYPE: Journal
LANGUAGE: English
OTHER SOURCE(S): CASREACT 66:37887
GI For diagram(s), see printed CA Issue.
AB The synthesis of a series of N-amidino-3-amino-5-substituted-6-halopyrazinecarboxamides (I) is described In rats and dogs, these compds. cause diuresis and saluresis while K excretion is unaffected or repressed Compds. with a variety of 5 substituents including hydroxy, alkoxy, mercapto, alkylmercapto, amino, and substitute amino were prepared The latter 2 tupes embrace compds. with the highest activity. Several routes for the synthesis of Me 3-amino-5,6-dichloropyrazinoate, a key intermediate, are presented. 23 references.
IT *14229-20-0P*
RL: SPN (Synthetic preparation); PREP (Preparation)
(preparation of)
RN 14229-20-0 CAPLUS
CN Pyrazinecarboxamide, 3,5-diamino-6-chloro-N-[imino[(3-pyridinylmethyl)amino]methyl]-, dihydrochloride (9CI) (CA INDEX NAME)



●2 HCl

L4 ANSWER 20 OF 20 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 1965:82636 CAPLUS
DOCUMENT NUMBER: 62:82636
ORIGINAL REFERENCE NO.: 62:14698f-h,14699a-h,14700a-h,14701a-h,14702a-b
TITLE: Substituted guanidines
INVENTOR(S): Cragoe, Edward J., Jr.
PATENT ASSIGNEE(S): Merck & Co., Inc.
SOURCE: 99 pp.
DOCUMENT TYPE: Patent
LANGUAGE: Unavailable
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
BE 639386		19640430	BE	
PRIORITY APPLN. INFO.:			US	19621030

GI For diagram(s), see printed CA Issue.
AB A suspension of 765 g. Me 3-aminopyrazinecarboxylate in 5 l. C6H6 was treated with 1.99 l. SO2Cl2, refluxed for 5 hrs., and left overnight at room temperature to give 888 g. crude Me 3-amino-5,6-dichloropyrazinecarboxylate (I), m. 233-4°. Into a solution of 100 g. I in 1 l. dry Me2SO dry NH3 was passed under stirring at 65-70° for 45 min., then at 10° for 1.25 hrs. to give 82.5 g. Me 3,5-diamino-6-chloropyrazinecarboxylate (II), m. 212-13°. A mixture of 14.2 g. II, 9 g. Pd-C, 4 g. MgO, and 250 ml. MeOH was shaken under H for 18 hrs. at room temperature to give Me 3,5-diaminopyrazinecarboxylate (III), m. 252-4° (decomposition) (iso-PrOH). Bromination of a suspension of 2 g. III in 25 ml. AcOH at 50° with 2.1 g. Br in 10 ml. AcOH gave 1.2 g. Me 3,5-diamino-6-bromopyrazinecarboxylate (IV), m. 217-19°. Hg(OAc)2 (3.2 g.) and a solution of 2.5 g. iodine in 20 ml. warm dioxane was added rapidly to a suspension of 1.7 g. III in 30 ml. H2O at 70°, the mixture heated for 5 min., cooled to room temperature, and treated with 50 ml. 15% KI solution precipitated 1.2 g. Me 3,5-di-amino-6-iodopyrazinecarboxylate, m. 200-2°. I (11.1 g.), 500 ml. iso-PrOH, 14.4 g. PhNH2, and 12.8 g. PhNH2.HCl was refluxed 24 hrs. under stirring to give 10 g. Me 3-amino-5-anilino-6-chloropyrazinecarboxylate, m. 171.5-73° (iso-PrOH). Similarly were prepared Me 3-amino-5-(p-chloroanilino)-6-chloropyrazinecarboxylate, m. 207-8° (MeCN), and Me 3-amino-5-dimethylamino-6-chloropyrazinecarboxylate (V), m. 145.5-6.5° (MeOH). A solution of 10 g. MeSH in 17 ml. 20% NaOH and 100 ml. MeOH was added to a boiling mixture of 17.7 g. I and 1 l. MeOH and refluxed 15 min. to precipitate 12 g. Me 3-amino-5-methylthio-6-chloropyrazinecarboxylate (VI), m. 212-16° (MeOH). VI (23.4 g.), 35 ml. 30% H2O2, and 300 ml. AcOH was stirred 18 hrs. at room temperature to give 18.5 g. the 5-methylsulfinyl analog (VII), m. 237.5-40.5° (decomposition) (MeOH-AcOEt-HCONH2). Hydrolysis of 7.5 g. VII in 75 ml. AcOH and 12 ml. H2O on a steam bath for 3 hrs. produced 3.7 g. Me 3-amino-5-hydroxy-6-chloropyrazinecarboxylate (VIII), m. .apprx.245° (decomposition) (HCONH2-EtOH). Hydrogenation of VIII with Pd-C and MgO at room temperature resulted in Me 3-amino-5-hydroxypyrazinecarboxylate, decompose 220-60°. Also were prepared Me 3-amino-5-dimethyl-aminopyrazinecarboxylate, m. 242.5-3.5°, Me 3,5-diaminopyrazinecarboxylate, m. 252-4° (decomposition), and Me 3-amino-5-methoxypyrazinecarboxylate, m. 205.5-7.5°. A mixture of 8.9 g. I and 20 ml. PhCH2NH2 was heated on a steam bath for 30 sec. to give 7.5 g. Me 3-amino-5-benzylamino-6-chloropyrazinecarboxylate (IX), m. 157-8° (MeOH). Hydrogenation of IX yielded Me 3-amino-5-benzylaminopyrazinecarboxylate, m. 189.5-91.5°. Treatment of 1.1 g. I with MeONa in 200 ml. boiling absolute MeOH produced 1 g. Me 3-amino-5-methoxy-6-chloropyrazinecarboxylate, m. 255-7° (MeCN). Na2S (9.6 g.) and 10 g. S was refluxed in 80 ml. absolute EtOH. Addition of 8.9 g. I at 25° and stirring for 1 hr. gave 7.8 g. Me 3-amino-5-mercapto-6-chloropyrazinecarboxylate, m. 207-8° (decomposition). To a refluxing solution of 4.44 g. I in 300 mil EtOH was added

guanidine (from 1.98 g. guanidine-HCl) in 50 ml. absolute EtOH in 15 min. and the mixture refluxed 0.5 hr. to give 3.1 g. Me 3-amino-5-ethoxy-6-chloropyrazinecarboxylate, m. 123-5° (iso-PrOH).
3-Amino-6-methylpyrazinoylamide (31 g.) was heated 10 min. with 320 ml. 10% NaOH. The resulting Na salt of the acid (97 g.) was methylated with 77 g. Me2SO4 in 700 ml. MeOH 19 hrs. at room temperature to give 18 g. Me 3-amino-6-methylpyrazinecarboxylate (X), m. 138.5-40.5° (C6H6). Chlorination of 9.2 g. X with 65 ml. SO2Cl2 under cooling produced 4.4 g. Me 3-amino-5-chloro-6-methylpyrazinecarboxylate, m. 108.5-10.5° (C6H6-cyclohexane). A mixture of 30 g. 3-amino-5-methylpyrazinecarboxylic acid and a solution of 30% HCl in 650 ml. MeOH was stirred 42 hrs. at room temperature to give 15.4 g. Me 3-amino-5-methylpyrazinecarboxylate (XI), m. 165-7° (H2O). A solution of 4.18 g. Br in 3 ml. AcOH was added to a solution of 4.2 g. XI in 15 ml. AcOH in 20 min. to produce 3.6 g. Me 3-amino-5-methyl-6-bromopyrazinecarboxylate, m. 179-81°.
Aminomalonamidamidine-2HCl (52.5 g.) was added to an ice-cooled solution of 28.8 g. ethylglyoxal in 450 ml. H2O. The mixture was made alkaline with .apprx.65 ml. concentrated NH4OH and left 20 hrs. at room temperature to precipitate 17.5 g.
3-amino-6-ethylpyrazinecarboxamide, m. 165.5-8.5° (iso-PrOH), which was saponified 30 min. on a steam bath with 10% NaOH to give 3-amino-6-ethylpyrazine-carboxylic acid (XII), m. 149-52°.
Stirring 14 g. XII in a solution of 33% HCl in 160 ml. MeOH 24 hrs. at room temperature gave 4.3 g. XII Me ester, m. 85-7° (iso-PrOH). Also prepared were 3-amino-6-p-chlorophenylpyrazinecarboxylic acid, m. 207-13°, and its Me ester, m. 181.5-3.5°. To a suspension of 17.9 g. 5,6-diaminouracil in 250 ml. H2O at 60° 14.9 g. cyclohexylgiyoxal-0.5 H2O was added and the mixture heated 1 hr. on a steam bath to give 7.5 g. 7-cyclohexyllumazine (XIII), m. 229-31° (aqueous AcOH). A solution of 18.5 g. XIII and 9 g. NaOH in 90 ml. H2O was heated in an autoclave 17 hrs. at 105° to give 8 g. 3-amino-5-cyclohexylpyrazinecarboxylic acid, m. 182.5-3.5° (aqueous iso-PrOH); Me ester m. 173-4.5°. Similarly were prepared Me 3-amino-6-cyclohexylpyrazinecarboxylate, m. 126.5-28°, Me 3-amino-6-cyclopropylpyrazinecarboxylate, m. 112.5-14.5° (amide m. 185.5-7.5°, free acid m. 169-72°), Me 3-amino-5-phenylpyrazinecarboxylate (XIV), m. 231-2°, and Me 3-amino-6-phenylpyrazinecarboxylate (XV), m. 140-1°. Chlorination of 25.6 g. XV with 90 ml. SO2Cl2 1.5 hrs. at room temperature gave Me 3-amino 5-chloro-6-phenylpyrazinecarboxylate, m. 187.5-91.5° (AcOH). Bromination of 10.5 g. XIV in 700 ml. AcOH with 11.2 g. Br 21 hrs. at 85° gave 10.5 g. Me 3-amino-5-phenyl-6-bromopyrazinecarboxylate, m. 217-21° (AcOH). To a suspension of 103.59 g. 4,5-diamino-2,6-dihydroxypyrimidine in 1500 ml. H2O and 500 ml. concentrated NH4OH at 60° 103.71 g. 1-phenyl-1,2-propanedione was added and the mixture heated at 90° under vigorous stirring to give 82.4 g. 6(or 7)-methyl-7(or 6)-phenyllumazine, m. 281.5-2.5° (AcOH), and 32 g. 6(or 7)-phenyl-7(or 6)-methyllumazine (XVI), m. 254.5-5.5°. Saponification of XVI with 8% NaOH in an autoclave 3.5 hrs. at 170° gave 3-amino-5(or 6)-phenyl-6(or 5)-methylpyrazinecarboxylic acid, m. 193.5-4.5°; Me ester m. 163-4° (MeOH). Similarly were prepared 3-amino-5(or 6)-methyl-6(or 5)-phenylpyrazine carboxylic acid, m. 155-6°; Me ester m. 162.5-3.5° (MeOH). Me 3-amino-6-phenylpyrazinecarboxylate was chlorinated with SO2Cl2 to give Me 3-amino-5-chloro-6-phenylpyrazinecarboxylate, m. 187.5-90.5° (AcOH), and subsequently treated with Me2NH in MeOH to give Me 3-amino-5-dimethylamino-6-phenylpyrazinecarboxylate, m. 167.5-9.5° (MeOH). To 750 ml. AcOH and 3180 ml. H2O at 38°, 90 g. Me 3-aminopyrazinecarboxylate was added and Cl passed through in 25 min. to give Me 3-amino-6-chloropyrazinecarboxylate (XVII) m. 142° (decomposition) (H2O). A solution of 18.8 g. XVII, 15 g. PhNH2, and 2.5 ml. concentrated HCl in 150 ml. Me2CO was refluxed 16 hrs. to give 7.4 g. Me 3-isopropylideneamino-6-anilinopyrazinecarboxylate, m. 195.5-7.5° (iso-PrOH). A mixture of 9.3 g. 3-amino-5,6,7,8-tetrahydroquinoxaline-2-carboxylic acid and 230 ml. absolute MeOH of 10° was treated with 30 ml. concentrated H2SO4 in 1 hr. and left 24 hrs. at room temperature to give 1.6 g. the Me ester, m. 154-5° (1:5 MeOH-H2O). A solution of 60 g. 4-chloro-o-phenylenediamine in 60 ml. H2O and 50 ml. 12N HCl was treated with a solution of 61.44 g. alloxan-H2O in 100 ml. H2O and stirred 1 hr. at 90° to give a precipitate of 78.4 g. 8-chloroalloxazine, m. 365-6° and 40.36 g. 7-chloro-alloxazine, (XVIII) m. 380° (Me2SO). A mixture of 44.2 g. XVIII and 190 ml. concentrated NH4OH was heated in an autoclave 10 hrs. at 165° to give 27.2% 3 amino-7-chloroquinoxalin-2-carboxylic acid, m. 191-2° (decomposition); Me ester m. 224.5-5.5° (MeCN). Also prepared are the following XIX (R, R1, % yield, and m.p. given): Me, H, 88, 221-2°; Et, H, 89, 149-50°; Pr, H, 75, 138-40°; iso-Pr, H, 70, 125.5-6.5°; CH2:CHCH2, H, 69, 105-6.5°; Bu, H, 91, 140-2°; sec-Bu, H, 75, 106-8°; iso-Bu, H, 51, 113.5-15.5°; tert-Bu, H, 38, 98-108°; Am, H, 72, 100.5-2.5°; MePrCH, H, --, --; Et2CH, H, --, --; C6H13, H, 70, 72.5-5.5°; cyclopropylnethyl, H, 78, 132-3° cyclopropyl, H, 98, 167-9°; cyclopentyl, H, 93, 119.5-21.5°; PhCH2, H, 64, 157-8°; p-MeC6H4CH2, H, 66, 112.5-14.5°; o-FC6H4CH2, H, 84, 171-4°; p-ClC6H4CH2, H, 93, 136-7°; PhCH2CH2, H, 59, 115-19°; CF3CH2, H, 97, 153-4° CF3CH2CH2, H, 76, 124.5-5.5°; HOCH2CH2, H, 100, 155-7°; HOCH2(CHOH)4CH2, H, 60, 172-5°; NH2CH2CH2, H, 96, 265°; Me2NCH2CH2, H, 40, 257°; 4-pyridylmethyl, H, 69, 95-7°; 2-furylmethyl, H, 81, 148-9°; Me, Et, 73, 102-4°; Me, Pr, 58, 83.5-5.5°; Me, iso-Pr, 78, 75.5-7.5°; Me, CH2:CHCH2, 70, 90.5-92°; Me, Bu, 74, 59.5-61.5°; Et, Et, 54, 99-101°; Et, Pr, --, --; Et, iso-Pr, --, --; Et, CH2:CHCH2, --, --; Et, Bu, 91, 77.5-9.5°; Pr, Bu,--, --; Pr, Pr, 66, 68.5-71.5°; (NRR1 =) pyrrolidino, 95, 168-71°; (NRR1 =) 1 (hexahydroazepinyl), 75, 109-11°; (NRR1 =) N'-Methylpiperazino, 88, 186-8°; Me, NH2, 67, 136.5-38°
Guanidine-HCl (XX) (26.3 g.) was added to a solution of MeONa (5.75 g. Na in 150 ml. absolute MeOH), the precipitated NaCl filtered off, and the filtrate concentrated to 30 ml. After addition of 11.5 g. V the mixture was boiled 1 min., then maintained 1 hr. at room temperature to give 93% (3-amino-5-dimethylamino-6-chloropyrazinecarbonyl) guanidine (XXa), m. 216-17°; HCl salt m. 298° (decomposition). Similarly were prepared (3,5-diamino-6-bromopyrazin-carbonyl)guanidine, m. 232.5-5.5° (decomposition), (3,5-diamino-6-iodopyrazinecarbonyl)guanidine-HCl, m. 273-4° (decomposition) and (3-isopropylideneamino-6-anilinopyrazinecarbonyl)guanidine, m. 214-16° (decomposition). To a solution of 920 mg. Na in 50 ml. absolute iso-PrOH 3.85 g. XX was added and the NaCl filtered off. Adding 4.4 g. I and refluxing the mixture 15 min. gave (3-amino-5,6-dichloropyrazinecarbonyl)guanidine HCl salt (XXb) m. 259-61°. The solution of XXb in 5 ml. HCONMe2 was treated with 1 ml. 25% aqueous Me2NH 1 hr. on a steam bath to give XXa. Reaction of 11.1 g. I with 55 ml. Me2NCH2CH2OH 20 min. on a steam bath gave 9.5 g. Me 3-amino-5-(2-dimethylamino-ethoxy)-6-chloropyrazinecarboxylate (XXI), m. 134.5-6.5° (C6H6-cyclohexane). To 20 g. XX in iso-PrONa (4 g. Na in 100 ml. iso-PrOH) 9.4 g. XXI was added and the mixture heated 30 min. on a steam bath to give 2.5 g. (3-amino-5-guanidino-6-chloropyrazinecarbonyl)guanidine-2HCl, m. >340°. A mixture of 2 l. concentrated NH4OH and 300 g. XVIII was stirred 16 hrs: at room temperature to give 260 g. 3-amino-6-chloropyrazinecarboxamide (XXII), m. 227-30°.
HC(OEt)3 (200 ml.) and 33 g. XXII refluxed in 200 ml. Ac2O 1.5 hrs. gave 20 g. 4-hydroxy-6-chloropteridine (XXIII), m. 268-70° (decomposition) (iso-PrOH). A solution of 5.5 g. XXIII and 4.4 g. PhCH2SH in 100 ml. 4% NaOH was heated 30 min. on a steam bath to give 5.5 g. 4-hydroxy-6-benzylthiopteridine, m. 233-5° (aqueous iso-PrOH), which was converted into 3-amino-6-benzylthiopyrazinecarboxylic acid (XXIV), m. 138-9°, by 8 hrs. hydrolysis with 5% NaOH. XXIV (8.5 g.) in 50 ml. Ac2O was heated 5 hrs. on a steam bath to give 6.6 g. 2-methyl-6-benzylthio-4H-pyrazino[2,3-d][1,3]oxazin-4-one (XXV), m. 116.5-18.5° (C6H6). To 1 g. Na in 30 ml. iso-PrOH 5 g. XX and 3.4 g. XXV were added to give,

after 1 hr. at room temperature, 1.1 g. (3-amino-6-benzylthiopyrazinecarbonyl-guanidine, m. 171-3° (decomposition). Similarly were prepared 4-hydroxy-6-methylthiopteridine, m. 289.5-91.5° (aqueous iso-PrOH), 3-amino-6-methylthiopyrazinecarboxylic acid (XXVI), m. 182-4° (decomposition) (AcOEt), 2-methyl-6-methylthio-4H-pyrazino[2,3-d][1,3]oxazin-4-one, m. 189-91° (C6H6), and 3-acetamido-6-methylthiopyrazinecarbonyl)guanidine (XXVII), m. 220-2°. Addition of HCl to XXVII in H2O gave 86% (3-amino-6-methyl-thiopyrazinecarbonyl)guanidine, m. 203-5°. A solution of 0.92 g. XXVI in 15 ml. 2.5% NaOH was treated with 1.05 g. KMnO4 in 35 ml. H2O to give 0.5 g. 3-amino-6-methylsulfonylpyrazine-carboxylic acid, m. 239-42° (decomposition) (iso-PrOH), which gave, after 5 hrs. heating in Ac2O, 2-methyl-6-methylsulfonyl-4H-pyrazino[2,3-d][1,3]oxazin4-one, m. 214-16° (Me2CO), transformed into 27% 3-amino-6-methylsulfonylpyrazinecarbonyl)guanidine, m. 224-6° (decomposition) (iso-PrOH). Similarly are prepared the following XXVIIa (R, R1, % yield, and m.p. given): H, H, 93, 240.5-1.5°; 293.5° (HCl salt); Me, H, 89, 238-9°; Et, H, 63, 217-18°; Pr, H, 93,221-2°; iso-Pr, H, 75, 215°; CH2:CHCH2, H, 84, 213-14°; Bu, H, 65, 219.5°; Me-ETCH, H, 74, 208-9°; iso-Bu, H, 76, 221°; tert-Bu, H, 84, 222-3°; Am, H, 70, 215-16°; MePrCH, H, 89, 186.5-8.5°; Et2CH, H, 82, 209-11°; C6H13, H, 100, 194.5-6.5°; cyclopropylmethyl, H, 95, 220-1°; cyclopropyl, H, 85, 213-15°; cyclopentyl, H 65, 219-20°; PhCH2, H, 44, 206-9°; p-MeC6H4CH2, H, 57, 216-17°; o-FC6H4CH2, H, 100, 206-8°; p-ClC6H4CH2, H, 96, 225-6°; PhCH2CH2, H, 57, 199-202°; CF3CH2, H, 77, 232-3°; CF3CH2CH2, H, 65, 221-2.5°; HO-CH2CH2, H, 63, 272-3°; HOCH2(CHOH)4CH2, H, 68, 223-4°; NH2CH2CH2, H, 68, 311°; Me2NCH2CH2, H, 98, 192.4-4.5°; 4-pyridylmethyl, H, 64, 239-40°; o-furylmethyl, H, 92, 217-18°; Ph, H, 95, 246.5-8.5°; p-ClC6H4, H, 95, 276-8°; Me, Et, 92, 229-30°; Me, Pr, 97, 214-15°; Me, iso-Pr, 70, 207-8°; Me, CH2:CHCH2, 95, 207-8°; Me, Bu, 95, 208-9°; Et, Et, 75, 215°; Et, Pr, 92, 224-5°; Et, iso-Pr, 75, 207-8°; Et, CH2:CHCH2, 92, 208-9°; Et, Bu, 98, 200.5-1.5°; Pr, Pr, 100, 221-2°; Pr, Bu, 84, 215-17°; (NRR1 =) pyrrolidino, 90, 244.5-5.5°; (NRR1 =) 1-hexahydroazepinyl, 49, 224-5°; (NRR1 =) N-methylpiperazino, 74, 299-300°; Me, NH2, 92, 234°.

Also prepared are the following XXVIIb (X, Y, % yield, and m.p. base and m.p. HCl salt given): H, HO, 10, >310° (decomposition); H, NH2, 8, 286-8° (decomposition), --; H, NMe2, 45, 224-5° (decomposition), --; H, MeO, 52, --, 229-30° (decomposition); H, PhCH2NH, 56, --, 231-7° (decomposition); Cl, MeO, 90, --, 257°; Cl, MeS, 100, 234.5-6.5°, --; Cl, HO, 24, --, >300° (decomposition); Cl, SH, 100, 236.5° --; Cl, EtO, 81, 215-16° --; Cl, Cl, 72, --, 259-61°; Me, H, 87, 218-19 (decomposition), --; Me, Me2N, 42, --, 262° (decomposition) (di-HCl); H, Me, 13,210° (decomposition), --; Me, Me, 38, 245° (decomposition), --; Br, Me, 35, 288° (decomposition), --; Et, H, 53, 207.5-9.5° (decomposition), --; H, cyclohexyl, 71, 221-2° (decomposition), --; cycloheptyl, H, 61, 228-30° (decomposition), --; cyclopropyl, H, 61, 196.5-99° (decomposition), --; H, Ph, 51, 224-6° (decomposition); Ph, H, 34, 194.5-5.5° (decomposition), --; Ph, Ph, 87, 234.5-5.5°, -; Ph, Cl, 69, 214-16° (decomposition), --; Br, Ph, 66, 234-6° (decomposition), --; p-ClC6H4, H, 70, 282-5° (decomposition), --; Me (or Ph), Ph (or Me), 77, 212-13° (decomposition), --; Ph (or Me), Me (or Ph) 90, 218-19° (decomposition), --; Ph, Me2N, 40, 205-6° (decomposition), --; (XY =)(CH2)4, 29, 220-1°, --; (XY =) CH:CHCH:CH, 56, 211-13°, --; (XY =) HC:CClCH:CH, 70, 246-7° (decomposition), --. A solution of 13.9 g. 2-methyl-2-pseudothiuronium sulfate (XXVIII) and 9.2 g. H2NCH2CH2OH in 40 ml. H2O was heated 20 min. to give 12.5 g. (2-hydroxyethyl)guanidine sulfate, m. 127.5-35.5°, which was added to a solution of 2g. Na in 25 ml. MeOH, MeOH distilled, and the residue treated with 4.1 g. II 5 min. on steam bath to give 1.2 g. 1-(3,5-diamino-6-chloropyrazinoyl)-3-(2-hydroxyethyl)guanidine-HCl, m. 228.5-9.5° (aqueous iso-PrOH). 1-(3-Amino-5-isopropylamino-6-chloropyrazinoyl)-3-(2-hydroxyethyl)guanidine-HCl.0.5H2O, m. 185-6° (decomposition), was prepared from Me 3-amino-5-isopropylamino-6-chloropyrazinecarboxylate. A mixture of 6.1 g. II, 6.8 g. phenylguanidine, and 3 ml. iso-PrOH was heated 6 hrs. to give 1-(3.5-diamino-6-chloropyrazinoyl)-3-phenylguanidine, isolated as the MeSO3H salt, m. 272° (decomposition) (H2O). Ph-CH2NH2 (80.3 g.) and 69.5 g. XXVIII in 200 ml. H2O kept 18 hrs. at room temperature gave benzylguanidine sulfate, which was converted into the HCl salt (XXIX) (51.5 g.), m. 175-8° (aqueous EtOH), by treating its aqueous solution with aqueous BaCl2. To a solution of 1 g. Na in 30 ml. iso-PrOH 9.3 g. XXIX was added and half the volume distilled Addition of 2 g. II and heating the mixture 15 min. yielded 1 g. 1-(3,5-diamino-6-chloropyrazinoyl)-3-benzylguanidine, m. 215-16° (decomposition) (aqueous iso-PrOH). With the appropriate starting materials the following 3-substituted 1-(3,5-diamino-6-chloropyrazinoyl)guanidines were prepared [3-substituent and m.p. (decomposition) given]: p-fluorobenzyl 216-19.5°; α-methylbenzyl 153-60°; 3-pyridylmethyl, 280.5-3.5°; 2-naphthylmethyl 243.5-5.5°. Also prepared were the following RR1-NC(:NH)NH2.HCl (R, R1, % yield, and m.p. given): p-Me-C6H4CH2 H, 28, 153-5°; o-ClC6H4CH2, Me, 32, 122.5-5.5°; PhCH2, H, 71, 131-6°; p-ClC6H4CH2, H, 55, 162.5-4.5°; p-MeOC6H4CH2, H, 69, 132-7°; 2,4-Me2C6H3CH2, H, 52, 105-15°; 2,4-Cl2C6H3CH2, H, 67, 145-8°; 3,4-Cl2C6H4CH2, H, 77, 155-7°; PhCH2CH2, H, 71, 135-8°.

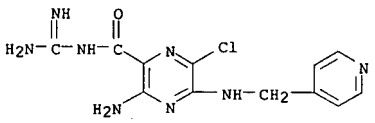
Also prepared were the following XXIXa [R, R1, % yield, and m.p. (decomposition)given]: p-MeC6H4CH2, H, 27, 210-12°; PhCH2, Me, 35, 274.5° (HCl salt); o-ClC6H4CH2, H, 39, 220-3°; p-ClC6H4CH2, H, 46, 204-6° p-MeOC6H4CH2, H, 27, 175.5-9.5°; 2,4-Me2C6H3CH2 H, 59, 220-2°; 2,4-Cl2C6H3CH2, H, 30, 267.5-70.5° (HCl salt); 3,4-Cl2C6H3CH2, H, 47, 216-19°; PhCH2CH2, H, 46, 219-21.5°. To a solution of 2.3 g. Na in 200 ml. absolute MeOH 15 g. dimethyl-guanidine sulfate was added, the mixture refluxed 1 hr. and cooled, Na2SO4 filtered off, the solution concd, to 30 ml., 10.15 g. II added, and the mixture heated 30 min. and kept 1 hr. at room temperature to give 3.6 g. 1-(3,5-diamino-6-chloropyrazinoyl)-3,3-dimethyl-guanidine (XXX), decomposing at 240° HCl salt m. 275° (decomposition). To a solution of 36.57 g. Et2NH in 100 ml. H2O and 41 ml. concentrated HCl adjusted, with 3.66 g. Et2NH to pH 9.2 a solution of 50% aqueous cyanamide (65.16 g.) was added dropwise at 100° in 4 hrs. After refluxing 1 hr. and standing over night at room temperature the mixture was treated with 50 ml. of 40% NaOH and CO2 passed through under cooling to give 1,1-diethylguanidine, isolated as the HCl salt (XXXI) (35 g.), m. 147-9°. Similarly, 1,1-dibutylguanidine-HCl (XXXII), m. 104.5-106° (H2O), was obtained in 86% yield. The following compds. were also prepared: 88.6% 1-(3,5-diamino-6-chloropyrazinoyl)-3,3-diethylguanidine, m. 265° (decomposition), from II and XXXI and 72% 1-(3,5-diamino-6-chloropyrazinoyl)-3,3-dibutylguanidine, m. 148-9° (iso-PrOH), from II and XXXII.

Also prepared were the following XXXIII (R, R1, % yield, and m.p. given): iso-Pr, H, 35, 238.5-40°; CH2:CHCH2, H, 39, 215°; Bu, H, 17, 187.5°; cyclopropylmethyl, H, 3, 196-7°; Me, Me, 69, 219°; Me, Et, 49, 218°; Me, iso-Pr, 61, 209-11°; Et, Et, 40,214°. The compds. are effective in the treatment of abnormal electrolyte excretion.

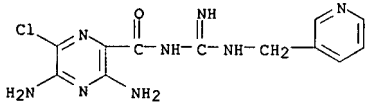
IT *1233-60-9*, Pyrazinecarboxamide, N-amidino-3-amino-6-chloro-5-[(4-pyridylmethyl)amino]- *1634-14-6*, Pyrazinecarboxamide, 3,5-diamino-6-chloro-N-[(3-pyridylmethyl)amidino]- (preparation of)

RN 1233-60-9 CAPLUS

CN Pyrazinecarboxamide, N-amidino-3-amino-6-chloro-5-[(4-pyridylmethyl)amino]- (7CI, 8CI) (CA INDEX NAME)



RN 1634-14-6 CAPLUS
CN Pyrazinecarboxamide, 3,5-diamino-6-chloro-N-[(3-pyridylmethyl)amidino]-
(7CI, 8CI) (CA INDEX NAME)



=> LOG HOLD

COST IN U.S. DOLLARS	SINCE FILE ENTRY	TOTAL SESSION
FULL ESTIMATED COST	103.58	271.57
DISCOUNT AMOUNTS (FOR QUALIFYING ACCOUNTS)	SINCE FILE ENTRY	TOTAL SESSION
CA SUBSCRIBER PRICE	-15.00	-15.00

SESSION WILL BE HELD FOR 120 MINUTES
STN INTERNATIONAL SESSION SUSPENDED AT 06:28:03 ON 19 OCT 2006